(2) human pathology
(3) hypertension
(4) arteriosclerosis
(5) periarteritis nodosa
(6) libman sacks disease
(7) leukemia
(8) myeloma
(9) neurocirculatory asthenia
(10) graves disease.
(15) achlorhydria
(17) anemia
(18) sprue syndrome
(19) emphysema
(20) psychosomatic medicine
(21) uremia (22) nephrosis

hyperkinetic diseases

# BIOLOGY
# OF
# DISEASE

MT. SINAI HOSPITAL

MONOGRAPH No. 1

# BIOLOGY OF DISEASE

*By*
ELI MOSCHCOWITZ, M.D.

*Physician, Mt. Sinai Hospital, New York;*
*formerly Assistant Professor, Clinical Medicine,*
*Columbia University.*




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# PREFACE

*The continued separation of disease into types can be pressed too far, and a subdivision which may perhaps have some immediate practical use can help to conceal underlying mechanisms held in common and thus to hinder progress in studying disease.—Sir Thomas Lewis*

When chronic disease is closely observed one appreciates that many diseases are not sharply defined genera but transitions of morbid states from one to another. Much of the differentiation that has resulted from more refined observation and more detailed laboratory investigation has tended to confuse rather than to simplify the issue and has caused the classification of disease to be more artificial than biologic. Too often diseases are classified according to a mere grouping of signs and symptoms, rather than in relation to a precise etiology or a well observed consistent pathogenesis. Many chronic diseases, like biologic species, present an evolution from the primitive or embryonic to a full-fledged form. It would be just as consistent to classify the earliest, the intermediate and the final phases of disease as separate entities as it would be to classify the tadpole and the frog as different species.

Most of the confusion in classifying disease comes from an ignorance of the causes of disease. As long as the cause of many chronic maladies is unknown, so long will one be forced to classify disease on the basis of clinical differentials. This does not mean, however, that mere modification of disease processes require separate classification. Time and again conditions that are regarded as separate disease entities eventually prove to be only biologic sports or mutations.

It is not generally realized that those whose entire medical experience centers in hospitals and consultation work see only a small cross section, usually the terminal one of the disease. Of the previous life cycle of the disorder they are ignorant; at best the previous cycle may sometimes be painfully reconstructed. To be able to follow a malady from the beginning to the end is the special privilege of the practitioner and the problem of unraveling the evolution of morbid processes is his. MacKenzie recognized this years ago, and the institute in St. Andrews, in which the very beginnings of disease are studied, is the outcome of his reflections.

In the absence of a knowledge of etiology, one of the best bases for the classification of chronic disease is a uniform and consistent pathogenesis. One may even be unaware of the precise progress of events, of a correct teleologic inter-

pretation, but one is safe in saying that maladies that have the same pathogenesis are usually intimately related. At the outset, therefore, diseases may be classified into two great divisions. Those which have a well established pathogenesis possess the dignity of a distinct genus or disease; those which have been classified on the basis of a mere grouping of clinical phenomena are syndromes.

This question of evolution of morbid states is not merely a matter of correct interpretation. Current statistics on nosology lose much of their significance, or even all of it, because the recording clinician did not note in what phase of the process the symptom or sign occurred. One might as well try to correlate a number of unrelated variables.

Studies in this direction will tend to synthesize disease complexes rather than disintegrate them, as has been the custom in the past.

The essays that follow cover only a small field in internal medicine, and the topics were selected because the biological nature of most of the diseases discussed is not too obvious. Although chronic disease lends itself particularly to a biological study, since the time factor is comparatively long, most acute diseases may be studied in the same manner. Witness, for instance, the wide range of potential clinical evolutions of such acute maladies as rheumatic fever and pneumonia. Our main purpose in these essays is to stimulate a point of view and a methodology rather than to be strictly informative and to emphasize the dynamic as opposed to the static approach in the study of disease. Relativity has its field in medicine as well as in physics.

I am grateful to C. V. Mosby for permission to republish the article written by Dr. S. S. Bernstein and myself on "The relation of neurocirculatory asthenia to Graves' disease" from the American Heart Journal, vol. 28, pages 177–198, 1944, and to Lea and Febiger to republish my article on "The hyperkinetic diseases" from the American Journal of Medical Sciences, volume 206, pages 576–599, 1943. This latter chapter has been included in its entirety because, although some of the subjects with which it deals have been discussed separately in preceding chapters, these are now treated as a group in order to demonstrate the relation of hyperkinesis to their development. Most of the remaining articles appeared as a series in the Journal of the Mount Sinai Hospital, which has kindly granted permission to republish them in this volume.

E. M.

# CONTENTS

CHAPTER 1

# HYPERTENSION OF THE PULMONARY CIRCUIT

In a series of 770 consecutive autopsies (1) I found arteriosclerosis of the pulmonary artery in 6.5 per cent. Moreover, if simultaneous observations upon the incidence of gross sclerosis of the aorta and pulmonary artery are made, a remarkable circumstance is discovered that appears to have been hitherto overlooked, namely, that they are completely independant. In other words, arteriosclerosis may be present in the pulmonary artery with complete absence in the aorta and vice versa. As a matter of fact, the simultaneous presence of gross arteriosclerosis in both the pulmonary artery and the aorta is the exception rather than the rule. This independence in incidence furnishes, in my opinion, the strongest argument that the mechanistic factor, namely, intravascular pressure, is dominant in the production of arteriosclerosis.

When arteriosclerosis of the pulmonary artery is found, the following underlying conditions are present.

1. Mitral disease, either stenosis or insufficiency. This is by far the most common.
2. In permanent emphysema whether secondary to asthma or to senility.
3. In any lesion of the lungs that causes widespread obliteration of the parenchyma, such as fibroid tuberculosis, bronchiectasis, pulmonary abscess, interstitial pneumonitis (e.g. silicosis), carcinomatous lymphangitis (Greenspan (2)) or widespread pleural adhesions.
4. In cardiac disorders that lead to prolonged right heart failure, for instance, coronary disease, adherent pericardium, "spent" Graves' syndrome or kyphoscoliosis.
5. In open ductus Botalli or other shunts between the right and left hearts, but only when the shunt is from left to right.

Under no other conditions with the rare exception of a decrescent lesion that only occurs in senility, does arteriosclerosis of the pulmonary artery occur.

Arteriosclerosis of the pulmonary artery is independant of age and sex. It

occurs even during the first year of life (Zur Linden (3), Watjen (4)) in the presence of a congenital cardiac lesion. The lesions do not differ from those of arteriosclerosis of the aorta or of the larger trunks of the greater circulation except that atheroma is not so pronounced and calcification is rare. The lesions affect the larger branches and the arterioles simultaneously and are always accompanied by changes in the pulmonary capillaries in the form of dilatation and thickening of the walls (Moschcowitz (1), Parker and Weiss (5)) precisely comparable in morphology to those found in the glomeruli of the kidney in hypertension of the greater circulation. To these changes, the term, arteriocapillary fibrosis, employed by Gull and Sutton, may be aptly applied.

The common denominator in the conditions above named is an increase in the pulmonary vascular resistance, and while we regrettably have no method of measuring the pressure in the pulmonary artery*, we can predicate that on a purely mechanistic basis, the pressure within the pulmonary vascular circuit must be raised. A stenotic mitral valve causes an increased tension within the left auricle which is transmitted backward through the pulmonary veins and thence to the alveolar capillaries. In mitral insufficiency the tension in the left auricle is increased through regurgitation into this cavity. In emphysema, the increased resistance is the result partly of extensive destruction of the capillary bed and partly by compression and stretching of the interalveolar arterioles due to the expansion of the alveoli (Cloetta (6)). Extensive chronic infiltrations of the lung cause an increased peripheral resistance by the destruction of a considerable part of the capillary bed. Failure of the right heart may be direct as the result of mitral disease or indirect after primary failure of the left ventricle. When the left ventricle becomes insufficient, there is an incomplete discharge of blood; as a result the left auricle cannot discharge itself completely, and the blood dams backward through the pulmonary veins resulting in an increased resistance to the flow of blood from the right ventricle. In communications between the two sides of the heart (when the shunt is from left to right) the increased resistance is due to the increased quantity of blood thrown into the right heart through the open communication. The explanation for the increased resistance in the pulmonary circuit following advanced kyphoscoliosis is not entirely clear. It is partly due to compression of the lungs by atelectasis and compensatory emphysema, to kinking of the pulmonary vessels, and to the attacks of repeated bronchitis to which these patients are subject. (Fishberg (7)).

These mechanisms fulfill the requirements of Wiggers (8) for the production of hypertension of the pulmonary circuit: 1) minute output of the right ventricle, 2) resistance and capacity changes in the pulmonary circuit, 3) back pressure resistance produced in the left heart by changes in the systemic circuit.

Whether there is a primary sclerosis of the pulmonary artery is very much open to question. I (9) have already discussed the matter in the past. The number of reported cases are few, and when sufficient data are at hand, by

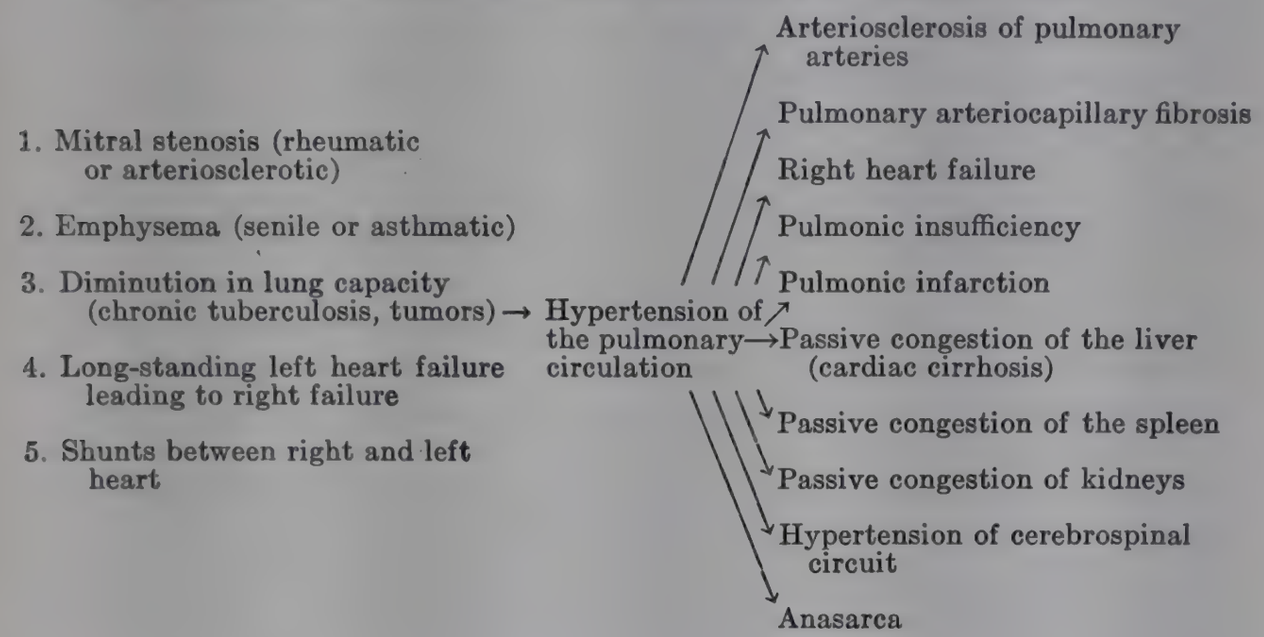
*Since this was written, Cournaud's method by direct catheterization of the right heart has proven successful.

far the majority of reported cases do not pass a strict critique. This applies especially to the much quoted cases of Ayerza's disease, which on strict analysis deserves no recognition for it is in no sense a primary arteriosclerosis but is a condition secondary to various pulmonary lesions. Moreover, there is no proof that it is syphilitic.

*The clinical evolution of hypertension of the pulmonary circuit*

The first consequence of clinical importance is anoxemia due to the interference of the passage of oxygen because of the increased thickness and fibrosis of the capillaries of the alveolar wall. In shunts between the right and left hearts the anoxia is aggravated by the amount of unsaturated blood that is poured into the left heart. The anoxemia results in an increase in the percentage of reduced hemoglobin in the blood resulting in one of the conspicuous clinical

EVOLUTION OF HYPERTENSION OF THE PULMONARY CIRCUIT




phenomena of hypertension of the pulmonary circuit, namely, cyanosis. Lundsgaard and Van Slyke (10) have estimated that it requires at least 6 to 7 per cent mean capillary unsaturation of oxygen before cyanosis appears. When failure of the right heart ensues, the cyanosis is enhanced because of two superimposed mechanisms: the slowing of the peripheral capillary flow resulting in increased reduction and the increase in venous pressure. Goldschmidt and Light (11) have shown that cyanosis is in large part due to the subcapillary venous plexuses, even in the absence of capillary unsaturation.

The first compensatory result of the prolonged anoxemia is polycythemia, produced by a hyperplasia of the bone marrow.

The succeeding compensating mechanism is an increase in circulating blood volume. This is observable only in long standing cases of hypertension of the pulmonary circuit, especially those that have been through repeated attacks of failure. The mechanism is allied to the polyuria that follows progressive

renal insufficiency. For a long time, especially among hematologists, secondary polycythemia was differentiated from polycythemia vera by the fact that in the latter the blood volume was uniformly high while in secondary polycythemia it was uniformly low; but the transition in secondary polycythemia from a low to an elevated blood volume is altogether too common to be employed as a differential.

Parallel with the foregoing, other compensatory mechanisms following hypertension of the pulmonary circuit take place. First, progressive hypertrophy and eventually dilatation of the right ventricle. Second, dilatation of the pulmonary artery with the development of a pulmonary conus visible by x-ray. In long standing cases, the resulting dilatation of the pulmonic ring results in pulmonary artery insufficiency and the development of a Graham-Steele murmur. Occasionally, the dilatation of the main branches of the pulmonary artery may be so great as to produce dancing shadows at the hilum of the lung. This is particularly notable in cases of so-called primary dilatation of the pulmonary artery (Oppenheimer (12)). Third, concomitant with the sclerosis of the pulmonary artery there occurs sclerosis of the lining of those chambers of the heart that are subject to increased pressure. These are usually the left and right auricle and the right ventricle. In uncomplicated emphysema when the peripheral resistance is within the capillary bed, the left auricle is not involved. The pulmonary veins also, as a rule, become involved by phlebosclerosis, except of course in emphysema. In my observations, sclerosis of the lining of the left ventricle does not occur in hypertension of the pulmonary circuit except when the latter is secondary to some lesion that produces primary failure in the left ventricle, such as an aortic lesion, coronary sclerosis or hypertension of the greater circulation.

Eventually, in protracted cases of hypertension of the pulmonary circuit when the dilatation of the right ventricle becomes extreme, dilatation of the tricuspid ring ensues, resulting in a relative tricuspid insufficiency. Such an insufficiency is further enhanced by sclerosis and thickening of the valves, that goes hand in hand with the sclerosis and thickening of the endocardium.

Further anatomical consequences of hypertension of the pulmonary circuit are congestion of the viscera, especially of the lungs, liver, spleen and kidneys. These lesions are due primarily to venous engorgement but not necessarily, it should be emphasized, to an increased venous pressure. These morphologic changes do not as a rule affect the function of these organs in the compensated phase of hypertension of the pulmonary circuit.

In time, unless life is compromised by intercurrent disease, failure ensues due to the breaking down of the compensatory mechanisms. A circulatory balance is maintained for a long time because the right side of the heart compensates for the increased resistance by an increase in the amplitude of the contraction of the ventricle. But the initial tension, if continued, eventually stretches the ventricular walls beyond the point where a complete contraction is possible, and a certain amount of residual blood remains in diastole within the right ventricle, resulting in dilatation. This dilatation in turn forces the right auricle

to empty against a positive pressure and an increase in venous pressure results. A rise in venous pressure therefore is one of the earliest manifestations of right-sided cardiac failure and the degree of the elevation corresponds broadly to the degree of failure. Usually, right sided heart failure responds to therapy, but recurrences are the rule and in time the attacks become progressively less responsive, become more frequent and a time comes when a state of chronic failure persists. When this arises, a host of secondary and widespread physiological and morphological changes occur which are reflected clinically. These may be discussed topographically.

*a. Lungs.* The later stages of arteriocapillary fibrosis become manifest. The alveolar walls become greatly thickened with corresponding diminution in the size of the alveoli with resultant diminution in vital capacity. The fibrosis progressively increases and in exceptional instances, reversion to the embryonal type of lung takes place. As the result of a combination of the slowing of the blood stream, pulmonary engorgement and arteriosclerotic disease of the blood vessels, hemorrhagic infarcts are common which may remain as such or induce consolidation in greater or lesser areas. In the process of healing, infarcts may increase the fibrosis. These morphological changes result in an increasing anoxemia, cyanosis and polycythemia.

The dyspnea which in the compensated phases was exertional is now orthopneic. Hemoptyses are common and occasionally pneumonic consolidation ensues with its consequences.

*b. Pleura.* The cause for the development of hydrothorax in right-sided heart failure is in a large measure the resultant of the localized expression of general venous engorgement. But there must be other factors to account for its frequent unilaterality and especially for its common localization to the right side. A complete answer to this problem has not yet been adduced. For a discussion see (Fishberg (7)).

*c. Liver.* In chronic failure, the venous engorgement of the liver causes an increase in size. In my experience, enlargement of the liver sufficient to make it palpable does not as a rule occur in hypertension of the pulmonary circuit unless failure is or has been present, and the longer the history of failure, the larger the liver. The morphologic changes that take place in the liver in prolonged right sided cardiac failure are particularly pertinent in respect to the development of cardiac cirrhosis. The conventional explanation hitherto has been that cardiac cirrhosis is the result of a replacement fibrosis consequent to the atrophy pressure of the liver lobules that occurs around the dilated central veins. Some years ago (13) I submitted another explanation based upon the finding of phlebosclerosis of the hepatic veins. Such a sclerosis is only found in long standing cases of hypertension of the pulmonary circuit with a history of repeated attacks of failure. The only reasonable explanation for this phlebosclerosis is the prolonged elevated venous pressure within the hepatic veins transmitted backward from the inferior vena cava into the hepatic veins. Indeed, I pointed out at that time that increased venous pressure is the *sine qua non* for every variety of true phlebosclerosis found in the human organism. In my

interpretation, cardiac cirrhosis represents a capillary sclerosis due to the further transmission of the increased pressure in the hepatic veins directly into the communicating central veins. In other words, the mechanism is precisely analogous to the conditions encountered in the pulmonary circuit. In the liver the hepatic veins occupy the place of the pulmonary artery, while the capillaries around the central veins represent the capillaries of the pulmonary alveoli. The main differences between the two systems is that in one the main vessel is arterial while in the other it is venous and while in the former the blood flows away from the heart, in the liver it flows toward the heart; but these differences do not minimize the significance of the pressure changes. It remains a fact that cardiac cirrhosis of any degree at least, is never found unassociated with sclerosis of the hepatic veins, and in patients in whom a prolonged increase in venous pressure can be predicated. Some of the most pronounced instances of cardiac cirrhosis I have ever encountered occur in patients with constrictive pericarditis, in whom prolonged high venous pressures are the rule.

In the early stages of hypertension of the pulmonary circuit the engorged liver represents a compensatory phenomenon and serves as an important component of the various venous blood depots that act as a release for the increase in venous pressure. In the later stages, when cirrhosis has supervened this blood depot becomes considerably compromised and renders compensation more difficult to attain. Furthermore, as a result of the increased resistance engendered by the sclerosis of the intrahepatic capillary barrier, an increased pressure in the portal circuit ensues, and if sufficiently intense, ascites results.

Concomitantly with these changes, other functions of the liver become compromised. Thus with the bromsulfalein test, Jolliffe (14) found impairment of liver function in 90 per cent of his cardiac patients. The urobilinogen is usually increased in the stools and in the urine (Eppinger). Hyperbilirubinemia is the rule in advanced right-sided failure and in a broad way parallels the duration and the intensity of the failure. If sufficiently pronounced it produces jaundice.

*d. Spleen.* In the early stages of hypertension of the pulmonary circuit without failure, the organ is deeply congested and cyanotic; the venous sinuses are dilated and engorged with blood and while the organ is enlarged it is rarely palpable. When failure takes place, the organ enlarges considerably, but at the same time, fibrosis occurs of varying degrees depending upon the duration of the failure. The subsequent contraction neutralizes whatever enlargement the congestion may entail, which, in all likelihood, explains why palpable spleens in congestive heart failure do not occur as often as one would expect. Indeed, in long standing cases, the spleen may shrink to less than normal size (cyanotic atrophy.) When the spleen becomes palpable in congestive failure, cardiac cirrhosis is as a rule prominent. The cause of the splenic sclerosis is not clear, but in view of the pathogenesis of cardiac cirrhosis which we have submitted, the likelihood is strong that a similar mechanism holds in splenic sclerosis, namely an increase in the venous and capillary pressures.

*e. The kidneys.* It seems remarkable that even in prolonged right-sided

failure from uncomplicated hypertension of the pulmonary circuit, the morphology of the organ is so little unaffected. It is true that a slight increase in the intertubular connective tissue results but never in sufficient amount to produce any considerable degree of contraction. Obviously when right-sided failure is consequent to a previous left failure, the result of hypertension, more profound changes are found in this organ but these are consequent to the hypertension of the greater circulation. In pure hypertension of the pulmonary circuit, the function of the kidney is not affected, but when failure sets in, various manifestations of disordered renal function become manifest. The first evidence is oliguria accompanied by a high specific gravity of the urine. Whether the oliguria is the result of slowing of the blood flow, increased capillary pressure or venous congestion has never been precisely determined. In a considerable measure, oliguria is due to extrarenal factors, meaning thereby that fluid is shunted away from the kidney by development of edema. Proteinuria, even of considerable degree, is present in most cases of right-sided heart failure due, no doubt, to the increased permeability of the glomerular capillaries. Casts are usually present. Azotemia is by no means uncommon, especially in prolonged and advanced degrees of right-sided failure, and is always associated with marked oliguria. Likewise the excretion of phenolsulphonthalein is often diminished due again to the oliguria. As a rule, all these evidences of impaired renal function subside more or less promptly if compensation can be restored, but in advanced cases, one or more of them may persist.

*f. The central nervous system.* Strangely enough, little is known of the anatomical changes in the brain in uncomplicated right-sided heart failure following hypertension of the pulmonary circuit. Obviously there is venous congestion. Edema is usually slight or completely absent, even in the presence of marked peripheral edema. The explanation for this relative freedom from edema is baffling. The congestion or edema or both, when present, may cause an increase in the size of the brain. But marked anatomical changes in the cerebrospinal system are conspicuously absent. Without doubt, therefore, many of the symptoms of cerebral disorder in primary right-sided failure are the result of disturbances in function. I believe with Fishberg (7) that the psychoses so frequently observed in the terminal stages are largely the result of excessive dehydration.

The cerebrospinal fluid pressure in primary right heart failure is often elevated, due to the increase in pressure within the cerebrospinal veins. This was demonstrated by Friedfeld and Fishberg (16) in right-sided failure and by Kessler, Moschcowitz and Savitzky (17) in secondary right-sided failure following hypertension of the greater circulation.

*g. Subcutaneous tissues.* Peripheral edema is one of the prominent evidences of right sided failure. In the early phases, the edema is latent and indirectly proportionate to the diuresis obtained by therapy. There is abundant evidence that, in the largest part at least, the edema is due to the increased hydrostatic pressure in the venous end of the capillaries which overcomes the neutralizing effect of colloidal osmotic pressure of the plasma. When the edema is of long

standing, a hypoproteinemia results due to the loss of protein that has escaped into the subcutaneous tissues, contributing to the already existing peripheral edema. A further reduction of the blood protein may occur as the result of a persistent and considerable proteinuria or an inadequate protein intake, or frequent tapping of pleural or abdominal exudates. Increased permeability of the capillaries may be a factor in the production of subcutaneous edema, because as Landis (18) has shown, anoxemia of even short duration renders the capillary more permeable to protein. However, as Fishberg (7) argues, permeability of the capillaries cannot be a factor of significant importance because the protein content of the edematous fluid in right heart failure is low.

The capillaries at the base of the finger nail, viewed by the Lombard-Mueller method are considerably dilated in hypertension of the pulmonary circuit. The dilatation is aggravated when failure arises.

*h. The left heart.* While failure following hypertension of the pulmonary circuit is more frequent following left-sided failure than the primary type, left-sided heart failure following right is, in my experience, exceedingly rare as a pure form. Usually both right and left-sided heart failure are associated. There are two possible explanations for the effect upon the left ventricle by failure of the right: 1) A sustained and progressive rise of effective venous pressure must eventually influence the work of the left ventricle. According to Starling and his co-workers (19), the left ventricular muscle increases its stroke volume. This inevitably leads to hypertrophy and eventually to dilatation. An increased left ventricular discharge is necessarily followed by an increased discharge of the right ventricle so that a vicious circle is established that takes its toll upon both sides of the heart. 2) The anoxemia must augment the work of the left ventricular muscle that is already overburdened by an increased venous return. Such a heart requires more oxygen than normal but the amount falls short owing to reduction in coronary flow that accompanies dilatation and hypertrophy of the left ventricle. (Hyde (20), Marowitz and Lahn (21)). In this way, another vicious circle is set in motion.

Disturbances in function of other organs, for instance, the *pancreas*, *adrenals* or the *ductless glands* are not detectable with present methods.

This discussion of the effects upon the organism of primary hypertension of the pulmonary circuit, both compensated and decompensated, cannot be concluded without a word or two upon the effect on the basal metabolic rate. That the basal metabolic rate is normal in the compensated phases of cardiac failure and elevated in the decompensated phases is a well attested clinical observation. The increased oxygen consumption is due, in large part at least, according to DuBois (22) to the dyspnea and the increased work of the respiratory muscles. In edematous patients with little or no dyspnea, I have found that the basal metabolism is sometimes low, reaching sometimes minus 30 per cent. The explanation for this curious phenomenon, as was pointed out some years ago (23) is the fact that the edema acts as a "suit of clothes" preventing the dissipation of heat.

It is necessary to emphasize that it is not the sclerosis of the pulmonary

arteries that is responsible for the clinical evolution, but the hypertension of the pulmonary artery that has produced this sclerosis. In other words, the sclerosis is the result and not the cause. Primary sclerosis of the pulmonary artery, as I have pointed out already, is rare, if it exists at all. The only manner whereby the sclerosis can contribute to the clinical picture is the predisposition to thrombosis and infarction.

Furthermore, hypertension of the pulmonary circuit and right-sided failure must not be confused, no more than hypertension of the greater circulation and left-sided heart failure. Failure is sequential to the hypertension.

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CHAPTER 2

# HYPERTENSION OF THE GREATER CIRCULATION

In a recent publication (1) the following currently recognized causes of hypertension of the greater circulation were discussed: 1) psychological; 2) sequelae of persistent Graves' syndrome; 3) renal disease; 4) adrenal blastomata or paragangliomata; 5) congenital peripheral resistances; 6) increased intracranial pressure; 7) carotid sinus dysfunctions; 8) lead poisoning; 9) Cushing syndrome. Of these all but the first two represent processes in which morbid anatomy comes first and hypertension follows. In the hypertension of psychologic origin or in that following persistent Graves' syndrome, the hypertension is primary in the sense that it is the first clinical manifestation and for this reason the term essential hypertension has been applied.

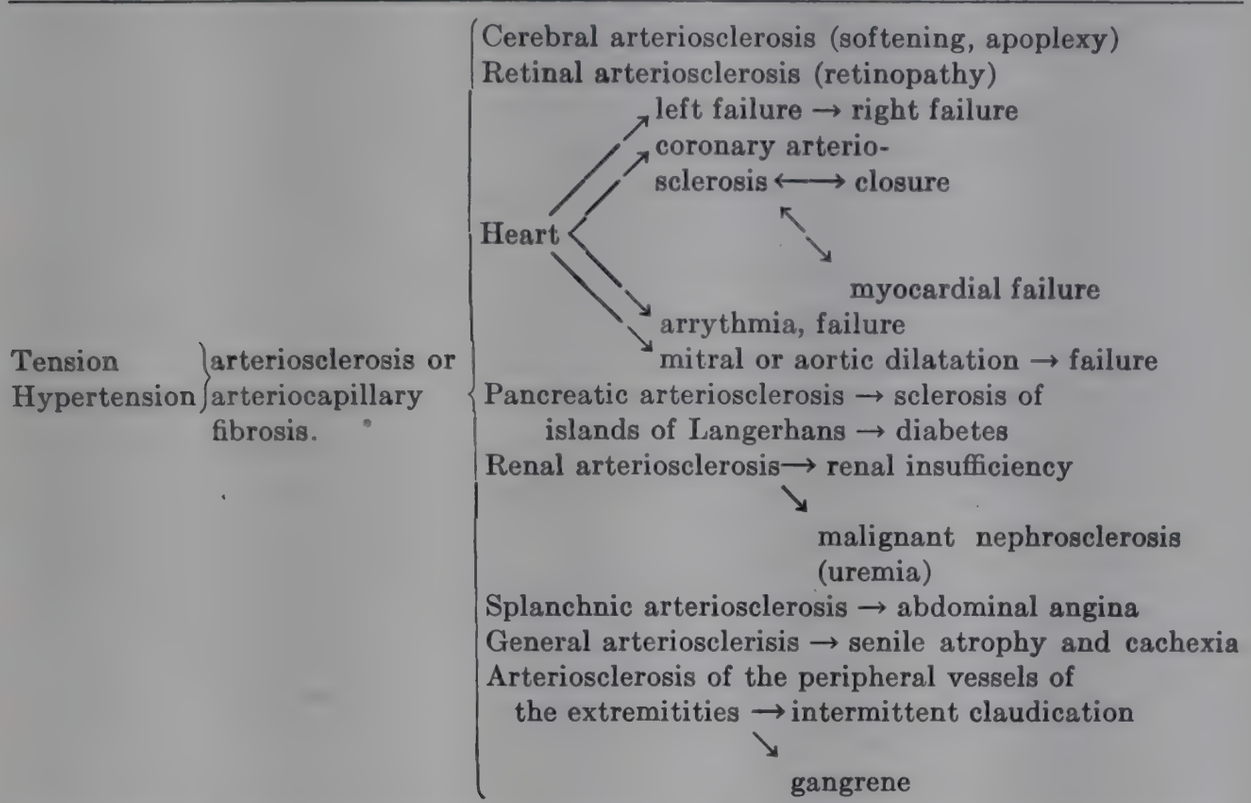
Elsewhere (2) I have discussed more fully the attributes of patients with essential hypertension. Psychically, they represent the antithesis of the child in mental make-up. They do not play and they do not exercise. They live compact, crowded lives with none or few avocations; they are insecure, mentally inelastic, look far forward into the future and so construct their life plan. Their mental horizon is narrow but within this range they pursue their aims with a grim determination. Physically, individuals with hypertension tend to be short, small necked, stocky individuals, unathletic in type and usually overweight but not necessarily obese. Statistics are eloquent (3) that weight is a conditioning influence upon the development of hypertension, especially with advancing years. Testimony is strong that there is a familial tendency to develop hypertension (O'Hare, Walker and Vickers (4), Weitz (5)) but how far this is the result of genotypic or environmental influences it is difficult to say. There has been a definite increase in incidence of hypertension in the last few decades, if one may judge by the present appalling increase in mortality from the cardiovascular-renal syndrome. I believe this increase is the result of the increasing stresses and strains, economic and social, that modern civilization entails. As evidence, we cite the striking increase in hypertensive disease in the northern Negro, whereas in the heart of Africa hypertension is almost unknown (Donnison (6)).

In other words, essential hypertension, like an infection, is the result of a

background and an insult. There has been a strong trend in recent years to view essential hypertension as a psychosomatic disease.

The biologic evolution of essential hypertension is manifold. Clinically it is manifested by one or more evidences of the cardiovascular-renal syndrome which is a compound of a host of anatomical and functional characters. The latter are partly the result of the anatomical changes and partly due to the stresses and strains that the hypertension imposes upon the cardiovascular system.

TABLE




This table illustrates why the different evolutions of hypertension and arteriosclerosis are seldom biologically pure. Combinations of these manifestations are the rule rather than the exception.

Why one or the other organs should be predominantly involved in such a generalized process is an intriguing problem. The concept of *Organminderwertung* only begs the question. Nor has the problem of the different tempo ranging, in musical terms, from *adagio* to *presto* that hypertension undergoes, been satisfactorily explained.

The primary anatomical event is arteriosclerosis which at first is strictly limited to the vessels of the greater circulation. The proof that arteriosclerosis follows hypertension and does not precede it, lies, as I have pointed out in Chapter I, in the independence in incidence between arteriosclerosis of the greater and pulmonary circulation. Unfortunately, in the past the study of arteriosclerosis has been largely confined to the vessels of the greater circulation but if simultaneous observations are made upon the vessels of both circulations, it will be discovered that as a rule arteriosclerosis is present only in the greater circulation and not in the pulmonary and vice versa, and when both are present simultaneously it is the exception rather than the rule. Arteriosclerosis of the pul-

monary circulation is practically confined to the conditions I have outlined in Chapter I, namely, to mechanisms that produce an increased pressure in the pulmonary circuit, such as mitral disease, emphysema, a failing heart, etc. The argument has been frequently advanced that arteriosclerosis cannot be due to hypertension because it is so frequently present with normal pressures, the so-called "senile" or "decrescent" arteriosclerosis of Allbutt. These observers fail to consider that hypertension is not an absolute but a relative value and represents an exaggeration of the normal intravascular tension.

The reason why the pulmonary artery is comparatively free from arteriosclerosis is because the normal pressure in the pulmonary artery is only one-sixth that of the aorta (Starling (7)). Even when the pressure in the pulmonary artery is raised to its highest value, it probably never approaches the systemic pressure, so that if such pressures can produce gross arteriosclerosis of the pulmonary artery, there is every reason for assuming that the normal systemic pressure, given sufficient time, can produce arteriosclerosis of the greater circulation. In other words, arteriosclerosis in the anatomical sense is a normal involutionary process. Hypertension brings it sooner (accounting for practically all cases of juvenile arteriosclerosis) and intensifies the process.

These remarks apply only to what may be termed gross arteriosclerosis, that is, lesions that are visible to the naked eye, which are present in every human being after the twentieth year. (Mönckeberg (8)). Microscopically, arteriosclerosis may be said to begin at birth, a process that may be termed "physiological ageing." At birth, the intima of the elastic arteries is exceedingly thin, consisting only of an endothelial layer lying almost directly upon delicate elastic lamina. With age, the intima thickens from 6 microns at birth to 190 at the age of 70 (Schäfer (9)). Splitting of the elastica occurs as early as the second year (Hallenberger (10)) and progressively increases with age. The media also thickens with the growth of the body from 650 microns at birth to 1111 at the age of 70 (Schäfer (9)). These changes have been noted in most of the vessels of the body (for references see Moschcowitz (1)). Now the essential lesions of arteriosclerosis are thickening of the intima, splitting of the elastica and hypertrophy of the muscular coat, the last especially prominent in the presence of hypertension. (Atheroma, in my opinion, is only a facultative lesion in arteriosclerosis, as shown by its practical absence in arteriolosclerosis). These hyperplastic processes may therefore be regarded as the juvenile expressions of the matured lesions and represent compensatory mechanisms for the progressive increase in intravascular pressure that proceeds from birth to old age (Aschoff (11)). As evidence we cite the intensification of these processes in the presence of hypertension. The term "hyperplastic" arteriosclerosis (Evans (12)) is aptly applied. In other words, physiological ageing and functional adaptation merge imperceptibly into anatomical, but not necessarily into clinical disease.

Identical processes are at work in the genesis of phlebosclerosis. In every instance of true phlebosclerosis, a condition that causes an increased pressure within the vein may be predicated (13).

Furthermore, analogous processes and mechanisms are in evidence in the

capillaries of certain organs. Sclerosis of the capillaries has been especially studied in the lung, the kidney, the pancreas and in the liver. In the lung, especially, the biology of the lesion can be easily studied (13) in hypertension of the pulmonary circulation, from a simple dilatation with fibrosis and perhaps hyalinization of the walls of the alveoli in the earliest stages to extensive fibrosis and obliteration of the walls and perhaps reversion to the embryonal type of lung in the advanced phases. These capillary lesions are always accompanied by gross arteriosclerosis of the pulmonary vessels. In the pancreas, fibrosis and hyalinization of the capillaries of the islands of Langerhans are practically always associated with gross arteriosclerosis of the larger vessels. In the kidney, sclerosis and hyalinization of the capillaries identical in morphology to those in the lung and pancreas are exceedingly common especially in association with hypertension (14), and again is accompanied by gross arteriosclerosis of the renal vessels. In the liver, the capillaries around the central veins show sclerosis and is progressive not only with the duration of the malady, but also with the intensity of the hypertension of the pulmonary circuit as gauged by clinical standards. It is most pronounced, for instance, in tricuspid disease, when the pressure in the right heart must be unusually high. The intensification and spread of the capillary sclerosis is responsible, to my view, for the genesis of cardiac cirrhosis (15). This hepatic capillary sclerosis only occurs with hypertension of the pulmonary circuit, and the mechanism of its development is due to the transmission backward of the pressure into the vena cava, thence to the hepatic veins and finally to the capillaries around the central veins. Whenever this capillary sclerosis is marked, especially in the stage of cardiac cirrhosis, the hepatic veins show a marked phlebosclerosis.

In summation, the lesions in these organs represent a true arteriocapillary (or as in the liver, a venocapillary) fibrosis. The capillary lesions are in a large measure responsible for some of the clinical phenomena. In the lung, they undoubtedly contribute to the anoxemia due to the difficulty in the exchange of oxygen through the thickened capillary wall. In addition, by the narrowing and sometimes obliteration of the alveoli they reduce the vital capacity. In the pancreas, the lesions cause diabetes, in all likelihood by the diminished production of insulin. In the kidney, the lesions in the glomeruli contribute many of the phenomena of renal insufficiency; lowering of concentration, proteinuria and eventually azotemia. In the liver, the venocapillary fibrosis causes various degrees of hepatic insufficiency.

Whether the concept of arteriocapillary fibrosis can be applied to other viscera such as the brain, retina, heart, spleen and organs of internal secretion is a matter for future study but judging by analogy, the probability is strong that it does. The difficulty lies in the morphologic study of single capillaries. In the organs cited above the task is comparatively simple because the capillaries occur in isolated groups. At all events, clinicians are aware that all these organs supplied by the greater circulation in addition to those mentioned above are sometimes affected by disease, either singly or simultaneously, and they accomplish such results by either reducing the blood supply by thrombosis consequent

to disease of the lining and resulting occasionally in embolism, or by rupture of an affected vessel.

*A. Brain and cerebrospinal system.* The clinical phenomena are characterized by such symptoms as apathy, dullness, loss of memory, headache, dizziness, occasionally delirium, hallucinations and at times, the involutional psychosis of senility. If death comes as the direct result of cerebral arteriosclerosis, it usually comes through cerebral hemorrhage or thrombosis.

There is another complication in the cerebrospinal system that frequently follows hypertension of the greater circulation, namely hypertension of the cerebrospinal fluid as determined by the spinal tap. Clinically it is manifested by severe headache, occasional nuchal rigidity, increased peripheral reflexes, occasional slight exophthalmos, and usually papilledema. A few years ago, Kessler, Moschcowitz and Savitzky (16) studied the mechanism whereby this syndrome arose in hypertension and concluded that it was largely the result of an increase in the permeability of the cerebrospinal barrier as determined by the Walther-Hauptman test, and in occasional instances, a superimposed increase in venous pressure due to complicating cardiac failure. It rarely occurs except in so-called "malignant hypertension" or "malignant nephrosclerosis".

*B. Retina.* The changes in the retina in hypertension vary from a mild form in which increasing tortuosity of the arteries with compression of the veins is the only manifestation to the advanced form of retinopathy in which narrowing or even obliteration of the arteries, exudates, hemorrhages and papilledema are the features. It is generally agreed that the lesions of hypertensive retinopathy represent an arteriosclerosis of the retinal and choroidal vessels (Collins and Mayou (17)) and in my experience the graver forms of retinopathy, i.e., with exudates and hemorrhages, rarely occur unless a diastolic pressure of 120 mm. Hg has been maintained over a prolonged period. The systolic pressure seems to bear little or no relation to the retinopathy. Once a retinopathy has developed of the graver variety with hemorrhages and exudates, it is persistent and one can predict that death is not far off. The only exceptions are conditions in which a marked drop in diastolic pressure has resulted. I have witnessed disappearance of a retinopathy in acute glomerulonephritis, in eclampsia after delivery, and after bilateral sympathectomy for hypertension.

*C. Heart.* Cardiac involvement is responsible for the majority of deaths. There are a number of eventualities which may bring this about.

1. Left sided cardiac failure. When the primary compensatory adjustments of hypertrophy and dilatation eventually breaks down, the heart is no longer able to pump sufficient blood to provide for the continuous inflow from the right heart; the blood stagnates in the lungs and the classical picture of left sided failure ensues with oliguria, nocturnal dyspnea and orthopnea. The venous pressure is usually low.

2. Right sided failure. When attacks of left sided failure have continued for a period of months or years, a compensatory mechanism may again restore comparative well being by causing a hypertension of the pulmonary circuit with dilatation of the pulmonary arterial tree. In turn the right heart hypertrophies

and dilates but eventually the muscle breaks down under the continuous strain and the clinical picture of right sided failure ensues, with anoxemia, exertional dyspnea, cyanosis, increased venous pressure, prolonged circulation time, enlargement of the pulmonary conus, swelling of the liver, anasarca (see Chapter I). The nocturnal attacks of dyspnea and the orthopnea are now relieved but from now on the history is one of repeated attacks of failure with chronic invalidism. Hypertension thus brings into being a whole series of compensating mechanisms which, if the patient lives long enough, follow each other in orderly sequence, with intervals of failure. In both these types of failure, the mechanisms may be interpreted in terms of disordered function rather than of morbid anatomy. Bell and Clawson (18) report that in their series, 44 per cent of their cases died from myocardial insufficiency.

3. Coronary disease. In Bell and Clawson's series, 16 per cent died of coronary disease. Unless the patient dies in an attack of closure, coronary disease results in left sided failure and eventually right failure exactly as in 1 and 2.

4. Dilatation of mitral and aortic rings. Either aortic or mitral insufficiency may result, partly due to the dilatation of the left ventricle or of the aortic ring, and partly to sclerosis of the valve consequent to the increased pressure.

5. Arrythmias. Almost every variety of abnormal cardiac rhythm may follow hypertension with or without coronary disease; extra-systoles, auricular fibrillation, partial or complete heart block, nodal rhythm. These indirectly contribute to the production of cardiac failure. Ventricular fibrillation frequently ushers in sudden death.

*D. Pancreas.* Hypertension of the greater circulation and diabetes are common associations. Joslin (19) finds that 19 per cent of diabetics between 21 and 50 years of age, and 33 per cent of those over 50 have hypertension. Kramer's (20) figures inclusive of all ages is 39 per cent. That sclerosis and fibrosis of the islands of Langerhans and sclerosis of the vessels of the pancreas are usually associated is admitted (Opie (21), Cecil (22), Warren (23)) and the presumption is strong that they are the direct cause of adult diabetes by lessening the production of insulin. Diabetes cannot be the cause of arteriosclerosis because in cases uncomplicated by hypertension of the pulmonary circulation, the pulmonary vessels are perfectly free. As Joslin (19) points out, the most common causes of death in patients with diabetes, since the discovery of insulin, are arteriosclerotic manifestations.

*E. Kidney.* Some degree of nephrosclerosis nearly always follows essential hypertension varying from a minimal involvement in which only scattered glomeruli are involved to such an extensive sclerosis that only traces of normal renal architecture are preserved. Grossly, a host of kidneys may be placed in series, varying in size from normal to a kidney that weighs only a few grams. The latter may be fittingly termed an end result, and has passed through the intervening stages. It is generally agreed that the contracted phase is the result of progressive narrowing or occlusion of the terminal arteriosclerotic vessels (MacCallum (24)). It is not clear why the vessels of the kidney show more widespread arteriosclerosis than in the rest of the general vascular system

(Bell (14)). Probably all individuals with essential hypertension would develop contracted kidneys provided they lived long enough. Unfortunately about nine-tenths die either of a cardiac complication or an irrelevant disease, comparatively early in the life cycle of the disease, even in the initial phase (25). Only about one-tenth therefore die of renal insufficiency.

Clinically, these progressive morphologic changes are paralleled by varying degrees of renal insufficiency. The first effect is a loss in concentrating power thus interfering with the excretion of harmful substances (urea, electrolytes, phosphates, etc.). The organism compensates by an oliguria and so a progressive lowering of the specific gravity of the urine occurs until it attains a value of 1010 isotonic with the glomerular filtrate which is deproteinized plasma. This phase is called by Fishberg (26) the compensated phase of renal insufficiency. After this, the kidney can no longer pass sufficient urine to maintain the normal quota in the blood so that these substances accumulate causing disturbances in the acid base equilibrium and uremia. This represents the decompensated phase of renal insufficiency. Proteinuria sooner or later appears; it rarely is sufficient to give a hypoproteinemia with its consequences. Partly as the result of the phosphatemia and partly from the loss of calcium by way of the proteinuria (if of sufficient degree) a hypocalcemia results, to compensate for which, the parathyroid glands enlarge (Pappenheimer and Wilens (27)). The renal insufficiency may be aggravated by an associated cardiac failure.

The term "malignant hypertension or malignant nephrosclerosis" has been applied to that clinical expression of the disease where the terminal event is complete or nearly complete renal failure with "uremia". Nosologically some have conferred upon this expression the distinction of a separate entity because it usually occurs in younger subjects, has a more rapid tempo and morphologically is nearly always accompanied by necrosis of arterioles, especially in the efferent vessels of the glomeruli. That it is not a separate disease is shown by the following observations: 1) The rapid tempo is only apparent. The hypertension antedates the history as given by the patients by many years, as I have observed only too frequently. The patient dates the beginning of his disease from the time he was clinically incapacitated. 2) It occurs in older subjects not uncommonly. 3) The necrotic lesions occur not only in essential hypertension but with glomerulonephritis. In my observations, these lesions are nearly always accompanied by prolonged high diastolic pressures. This is in accord with the observations of Goldblatt (28) who obtained such lesions in experimental hypertension.

*F. Extremities.* Clinically, arteriosclerosis of the lower extremities in essential hypertension is manifested by a whole range of symptoms and signs varying from intermittent claudication to gangrene, depending on the degree of narrowing. The narrowing is often aggravated by the association of Mönckeberg's sclerosis which is exceedingly common in the lower extremities. Why the upper extremities are comparatively immune from the ravages of arteriosclerosis is problematic. "Diabetic" gangrene is strictly speaking an arteriosclerotic gangrene complicated by diabetes.

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CHAPTER 3

# ARTERIOSCLEROSIS

The term "arteriosclerosis" has at present a stricter connotation than formerly employed. It does not comprise all lesions of vessels that cause thickening of the walls; for instance: luetic arteritis, periarteritis nodosa, the lesions accompanying rheumatic fever, lupus erythematosus, subacute bacterial endocarditis, thrombo-arteritis obliterans and thrombo-angiitis obliterans. There is ample testimony that the medial calcification of Mönckeberg is a different disorder, although both are often associated. Arteriosclerosis however cannot be defined by a process of exclusion. A precise definition, as we shall see, is difficult for a number of reasons. First, because it is a summation of many processes, one or more of which may be absent; second, because arteriosclerosis represents a wide biological range, so that the variety, extent and intensity of the lesions vary with the senescence of the process; and third, because the development of the lesions is modified by the structure of the artery and its topographical peculiarity. Despite this complexity, there are certain common factors. 1) it is a progressive process beginning already at an early age; 2) it is irreversible; 3) hyperplasia of one or more coats is exhibited; 4) some degree of thickening is always present; 5) dilatation, elongation and deformity are present; 6) there is a loss in elasticity.

We therefore suggest the following definition: *Arteriosclerosis is a progressive and irreversible affection in which hyperplasia of one or more coats is a primary reaction, with deposition of collagenous, lipoid, hyaline and calcium as a secondary reaction, the totality of both components resulting in thickening, dilatation, deformity and loss of elasticity of the walls.* This definition applies particularly to the advanced lesions observable in the senescent years, but what constitutes the earliest stages of arteriosclerosis is still a matter of keen debate. The answer cannot be given without a study of the morphology and growth of vessels from intrauterine life to advanced years. Under such conditions it will become apparent that normal physiological growth merges so imperceptibly into morbid changes that it is impossible to determine where one ends and the other begins.

Regrettably, most studies on arteriosclerosis have been limited to the lesions of the larger arterial trunks. As I have pointed out previously, (1), the study of morphologically comparable lesions in the veins, the capillaries, the arterioles

and even within the chambers of the heart, throws light upon the genesis and significance of the component lesions comprised under the term "arteriosclerosis."

The earliest vessel in the human embryo is a simple tube of mesenchyme lined by endothelium. During the fourth month of intrauterine life, the arteries acquire their three main layers: the intima, media and adventitia, (2, 3, 4), and the different tissue elements of which the wall of the vessel is composed: the elastica, the smooth muscle and the connective tissue, are already differentiated. Henceforth, the structural development proceeds somewhat differently depending on whether the vessel is of the elastic type such as the aorta, or of the muscular type such as the brachial artery.[1] In the aorta during the fourth month, the intima consists only of endothelium lying directly on the thick internal elastic layer. The media consists of several layers of muscle fibres, interlaced with an abundance of anastomosing elastic fibres. The adventitia, a layer of embryonic connective tissue, is thicker than the media. At the end of embryonal life, a thin connective tissue layer in the intima becomes visible, while the internal elastic layer thickens and begins to split. The elastic network within the media increases greatly. The muscle elements also increase, but not proportionately to the elastic elements. The adventitia becomes narrowed.

In the muscular arteries, in the fourth month of intrauterine life, the intima again consists only of an internal elastic layer directly covered by endothelium. The comparatively thinner muscular media contains relatively few elastic fibres. Between the media and the adventitia a well circumscribed elastic layer is developed, the elastica externa. The adventitia consists of two layers, an outer of connective tissue and an inner containing elastic elements. This elastic layer is entirely missing in the aorta. At birth, the internal elastic layer becomes thicker. The medial circular muscular coat increases in width, and contains, as compared to the aorta, but few and thin elastic fibres which continue into the internal and external elastic layers. The inner elastic layer of the adventitia is greatly increased.

In post-uterine life, the vascular system, in contradistinction to most of other organs of the body, continues in the process of differentiation, and it is in the interpretation of these changes that difficulty arises as to when the physiological becomes pathological.

In the arteries of the elastic type, the inner elastic later shows a progressive splitting into two or three layers; on its inner aspect a musculoelastic layer appears, the components running longitudinally. Farther toward the lumen there is formed a thin layer of collagenous fibrous tissue containing delicate elastic fibres on which rests the endothelium. Most observers follow the nomenclature of Jores (5), who terms the split layer of the elastica intima the "hyperplastic intimal layer", and the collagenous fibrous elastic layer as "the regenerative connective tissue layer." These layers of the intima continue to increase in thickness, and are not fully differentiated until the 30th year.

[1] There is no hard and fast distinction between these two types. They merge into each other as one proceeds from the periphery to the aorta.

In arteries of the muscular type similar changes occur, except that the muscular components overshadow the elastic in growth. The elastica in the media grows but does not form distinct lamellae. In the intima a hyperplastic elastic layer of thin dimension develops, but a musculo-elastic layer does not arise except near the areas of exits of branching vessels. A connective tissue layer forms between the endothelium and the inner elastic layer of the intima.

Although the structural changes proceeding from intrauterine life to adulthood are somewhat different in these two kinds of arteries, the change is essentially one of degree rather than of kind, and for our purpose these differences are unimportant. It suffices to appreciate that there is a steady growth of both elastic and collagenous elements that proceeds uninterruptedly into maturity. Thus Foster (6) finds a progressive increase in elastic fibres up to the 35th year. A quiescent period then occurs for about 10 to 15 years, when degenerative changes, lipoid and calcareous, set in. The wavy contour of the elastic fibres is almost lost and the fibres stain differently with Sudan III, being converted into elascin (Unna). He did not find an actual loss of elastic tissue. That active growth of connective tissue is progressive in vessels of maturer years is a well attested observation, not only in the intima but in all the coats, including the adventitia.

In the light of the investigations of Winternitz and his co-workers (7), who found an extensive network of vasa vasorum in the walls of both normal and diseased vessels, arising both from the adventitia and the intima, it intrigues us to think that part at least of the formation of new collagenous tissue may be the result of blockage of these vessels, comparable to the process that takes place in the myocardium in coronary disease. In part, the increase with age is the result of lipoid deposits. An untoward growth of such connective tissue in respect to the age of the individual is regarded by some as the beginning of arteriosclerosis, but inasmuch as the amount of such growth possesses such a wide range in adult life, this differentiation is hardly justified, except in instances of juvenile arteriosclerosis.

These hyperplastic intimal changes have been viewed by some as the result of "wear and tear", an indifferent term that covers so wide a range of influences that it represents only a blanket indictment. More particularly, Aschoff (8) describes these changes as an adaptation to the increasing intravascular pressure that proceeds from birth to adulthood. This view we regard as amply justified on a number of grounds. 1. Under the influence of increased intravascular pressure within the greater circulation these hyperplastic changes are intensified. This is particularly striking in cases of so called malignant hypertension; 2. The independence in incidence, as I have pointed out (1), between gross arteriosclerosis of the pulmonary vessels and those of the greater circulation. Gross arteriosclerosis of the pulmonary circulation is practically never observed except in instances where an increased pressure within the pulmonary circuit can be predicated; in mitral stenosis, for example. The reason for the comparative absence of gross arteriosclerosis in the pulmonary circuit even in middle aged adults is due to the fact that the intravascular

pulmonary pressure is only one-sixth that in the aorta [Starling (9)]; 3. A marked retinopathy, which is recognized (10) as an arteriosclerotic process, is practically absent unless a considerable degree of hypertension of the greater circulation is present; 4. Phlebosclerosis, a lesion morphologically comparable to that of arteriosclerosis, arises only when a local or a general increase in intravenous pressure is present. This is nicely illustrated in phlebosclerosis of the hepatic veins (11), in the portal circulation (12), and in the venous segment of an arterio-venous aneurism (13). The remarkable freedom, under normal circumstances, of hyperplastic changes in the veins is readily understandable in view of the extremely low pressures that exist within the venous system.

Obviously, the time factor must be taken into consideration, even under conditions of intravascular pressures within the range of normal. In this connection it is interesting to note that in rats and mice such intimal hyperplastic changes are not found, while in comparatively long-lived animals such as horses and cows they are well marked; whereas in cats and dogs, whose life range falls in between these extremes, the changes are comparatively slight (14).

Fox (14) states that there is a distinct difference between the appearance of arteriosclerosis in the shorter-lived mammals and in longer-lived animals, such as birds; he also points out that animals which revealed arteriosclerosis at autopsy had been in captivity nearly twice as long as the average exhibition period for their order and family. As further evidence we may cite the fact that gross arteriosclerosis may be seen in the pulmonary artery of an individual of advanced age (usually past 70) even without an associated hypertension of the pulmonary circuit (15). Therefore, when hypertension enters, the normal hyperplastic intimal changes occur earlier, and are intensified. This accounts in every instance for juvenile arteriosclerosis in the greater circulation, and also in the lesser circulation, where it has been observed even in the first years of life in association with congenital cardiac defects (16, 17).

The crucial problem now arises as to when physiological aging ends and arterosiclerosis begins. While some observers recognize the difficulty of such a differentiation, (2, 19, 20) the vast majority, headed by Jores (21), hold that arteriosclerosis begins only when various forms of "degeneration" set in, especially fatty and, to a lesser degree, mucoid, calcareous, and hyaline. No difficulty in interpretation arises when these degenerative changes present themselves in a pronounced form, such as in gross artheroma, in extensive calcific deposits or marked hyalinization. Unfortunately, Jores and his followers have not taken into consideration the fact that these substances are already normally present at an early age, some of them even at birth, and the problem arises whether these profound expressions represent no more than exaggerations of normal trends, comparable to the physiological aging represented in the hyperplasia of the intima and elastica. Furthermore, these observers have failed to appreciate that hyperplastic changes alone may give rise to a morphological picture consistent with arteriosclerosis even in the absence of any "degenerative" changes whatever. This is notably evident in arteriolosclerosis. We shall discuss these "degenerative" changes in order.

a. Lipoid deposits are exceedingly common in children in the intima of the aorta, just above the cusps, and unassociated with any productive change. From the fourth year on these lipoid deposits are almost constant. In the second decade, they are distributed throughout the aorta, especially at the sites of stresses, for instance on the proximal side of the exits of the coronary and intercostal vessels [Zinserling (22)]. From the third decade onward, these lipoid deposits are deposited at other sites of the aorta, often haphazardly, but sometimes particularly prominent at the sites of the intervertebral discs (Westenhoffer) (23). Confluence of these lipoid areas leads to atheromata which penetrate more deeply into the vascular coats. There is excellent evidence that these lipoid deposits stimulate the growth of collagenous tissue, (24, 25, 26), accounting for part of the growth of this tissue in the advancing years. These lipoid areas resemble precisely, both in conformation and distribution, those produced by Anitchkow (24) in his feeding experiments; whether they ever regress in the human being is entirely conjectural.

There has been much debate as to whether these early fat deposits represent the true beginnings of arteriosclerosis. Jores and others believe they do not, and that one can speak of a genuine arteriosclerosis only when these deposits are associated with an intimal hyperplasia. Curiously, of all the varieties of "degenerations", why Jores should choose the lipoid as the essential characteristic of arteriosclerosis is difficult to discern. Inasmuch as he admits that such intimal hyperplasia is already evident in the earliest years of growth, we fail to see the validity of his definition unless we accept the fact that arteriosclerosis begins at birth, which he does not admit. On the other hand, it is highly questionable whether lipoid, either in the form of small plaques or atheromata, is a facultative or a necessary component of arteriosclerosis. In arteriolosclerosis, characterized by enormous thickening due to intimal hyperplasia, both of the collagenous and elastic components, together with hyalinization, lipoid changes do not occur except in the later stages (26). Even in larger vessels, sclerotic patches in the intima may occur without lipoid (27). It is imperative to emphasize, therefore, that a distinction should be made between the terms arteriosclerosis and atherosclerosis, terms unfortunately too often employed interchangeably.

b. Mucoid "degeneration" of arterial walls has also been regarded as a component of the arteriosclerotic lesion (28), but there is abundant and strong evidence, particularly demonstrable by chromotropy (Kresylviolet method) that it is already present in the embryo. In post-embryonic life it increases in quantity proportionately to the increase in both the elastic and connective tissue structure, and in adult life it is present in the media between the muscle cells and the elastic fibres (29, 30). In the smallest vessels chromotropy disappears. In this respect also, as in lipoid changes, one cannot distinguish between the physiological and the pathological.

c. Calcareous "degeneration", especially in massive form, is conventionally held as indicative of arteriosclerosis. However, calcium can be demonstrated in the intima and media, especially by the silver nitrate method even in the

earliest years of life (31). Jores (21) finds it even in the first year, especially in the vessels of the pelvis, and in the early years of life in the common iliac artery. After the tenth year it is found uniformly in the abdominal vessels and in the aorta. After the 20th year it is found in all the larger vessels (32). As Faber (33) has shown, these early fine deposits of lime are unassociated with any degenerative tissue changes, especially lipoid. What relation these early deposits have to the pronounced calcific deposits seen in elderly life, or to the process termed "medial calcification" of Mönckeberg [a process comparable to that produced experimentally by ergosterol (34) or adrenaline (35)] is speculative. In the study of vessels in the later periods of life, Klotz (36) finds that the calcification is a secondary process and bears a distinct relation to the lipoid content of the tissues. There is also no doubt that hyalinization predisposes to calcification. The tendency for calcium to deposit in dead or inert tissues and later to be transmuted to bone is well known (37, 38). Nevertheless, it is questionable whether calcification is an inevitable accompaniment of arteriosclerosis, unless again we assume that the earliest hyperplastic changes already represent the beginnings of the process.

d. Hyaline change is exceptional in the earlier years, although it is found in the arterioles of the spleen as early as the tenth year (39). In the sense that hyaline normally is not found at birth, it may be termed a "degeneration", although its significance in the body economy is not clear. Hyaline is a common lesion in aging arteries, especially in the arterioles (40), and is particularly prominent in hypertensives. It is also seen in the walls of capillaries that have been subjected to increased intracapillary pressure (41, 42). Nevertheless, hyaline is not necessarily a part of the arteriosclerotic process, but a facultative one, similar to the lipoid, mucoid and calcareous changes.

The hyperplastic intimal changes that we have outlined as occurring in the larger vessels are precisely duplicated in the smaller branches: in the kidneys (43), in the spleen (44), in the coronary vessels (45, 46, 47), in the brain (48), in the radial (49) and pulmonary arteries (50). Under conditions of increased intravascular pressure they come earlier and are intensified. The same processes occur in animals that reach an age comparable to that of man.

From this discussion, it is apparent that the dividing line between physiological aging and the lesions conventionally grouped under the term "arteriosclerosis" is indefinite and that one merges into the other. One cannot conceive of arteriosclerosis as an inflammatory process, as Virchow insisted, or as a metabolic disorder (except perhaps in respect to the lipoid component), but rather as a normal compensatory process or adaptation to various factors, of which the progressive increase in intravascular pressure is by far the dominant one. It is only in this sense that we may speak of "wear and tear."

The term "primary" arteriosclerosis has often been employed, with the implication that there is a "secondary" type. Curiously enough, the term "primary" has been confined entirely to those forms of arteriosclerosis of the pulmonary artery for which no cause is found, such as hypertension of the

pulmonary circuit. I have discussed this matter previously (1). On analysis of the very few reported cases, I question whether a "primary" arteriosclerosis of the pulmonary artery exists. In the sense that arteriosclerosis represents a compensatory adaptation, the terms "primary" or "secondary" have little significance. This applies particularly to "Ayerza's disease", a malady without the slightest nosological status.

In other words, arteriosclerosis is a process which begins at birth (and perhaps before) and is an inevitable destiny of mankind. The process may be influenced by other factors, for instance, intravascular pressures, feeding, perivascular stresses and fixations (1), congenital or acquired abnormalities, and undoubtedly other as yet unknown factors, but it never can be completely escaped. This obviously does not imply that clinical and anatomical arteriosclerosis are equivalent. Arteriosclerosis causes disease only when the circulation of a vital organ is seriously compromised or when the weakened wall ruptures.

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CHAPTER 4

# PERIARTERITIS NODOSA

Periarteritis nodosa is a morphological entity, and possesses only a minor clinical significance. The essential lesion is a fibrinoid necrosis of the media, with swelling of the wall, destruction of the elastic laminae and a perivascular infiltration with cells, which may be polymorphonuclear, sometimes eosinophilic, or histiocytes or both. There may be proliferation of the intima in the later phases. The destruction of the vascular wall often leads to aneurysm formation, leading to the formation of nodes in the course of the vessels. In early lesions this is not seen. Klemperer (1) believes that in the absence of aneurysm, the term "necrotizing arteritis" is more applicable. This however does not necessarily imply that it is a different lesion. The fact that both types of lesions are usually found simultaneously and that the aneurysm is often only of microscopic dimensions is an indication that the aneurysm represents a later stage, induced by prolonged intravascular pressure, either normal, or, as so frequently occurs in periarteritis nodosa, increased. As a rule the lesions are diffuse; in exceptional instances, the lesions may be localized (2, 3). The classical lesions are seen mainly in vessels that are just visible to the naked eye although microscopically the smaller arteries and the vasa vasorum of the larger arteries are affected. Whether the capillaries are affected has not been determined. The lesions reveal a progression from an early active stage to healing with scar formation. Fishberg (2) described what is probably the earliest phase in an individual whose clinical history began only 6 days before death. The lesion was characterized by a deposition of fibrin in the walls; the intima was thickened by endothelial hyperplasia and hyalin and the walls of the arteries, both media and intima were infiltrated with polymorphonuclear leucocytes and occasional eosinophile cells. It is significant that the characteristic infiltration of the adventitia was absent. There were no aneurysms. In other words, the lesions presented all the ear marks of an exudative inflammation, and whether the lesion proceeded from within outwards or reversely was not clear. Arkin (4) described four stages: 1. an alterative degenerative; 2. an acute inflammatory; 3. granulation; 4. scar tissue. The report of Baehr and Manges (5) is noteworthy because two stages, four months apart, could be studied. The first revealed an acute or sub-

acute lesion, while the second showed extensive fibrillar degeneration of the internal elastic lamina, fibrous replacement of the media and a compensatory thickening of the intima. Keegan's (6) observation is somewhat similar; the right kidney was removed for a supposed surgical kidney; the renal vessel showed the acute lesion of periarteritis nodosa with necrosis and perivascular infiltration with polymorphonuclear cells, monocytes and occasional eosinophiles. Three months later, the patient died from renal insufficiency without hypertension. The renal vessels of the remaining kidney showed healing changes characterized by fibrosis of the walls, a marked fibrous intimal thickening, organized and canalized thrombi and a strictly mononuclear perivascular infiltration.

Jager (7) reports three cases of periarteritis nodosa with long clinical histories; one of 37 months, in which healed lesions were present characterized by extensive intimal scars, some of which were atheromatous. One obtains the distinct impression that the cellular infiltration changes from a preponderant polymorphonuclear in the early stage to an exclusive round cell type in the intermediate. The final phase represents a maturation of these elements with fibrosis, hyalinization, intimal thickening, and either narrowing of the lumen or aneurismal formation which may be either microscopic or macroscopic. Frequently, the lesions are associated with thrombosis which organizes and sometimes undergoes recanalization. In view of the destructive nature of the lesion one would not expect a complete anatomical restoration to normal.

However, such cicatricial or anatomical healing does not necessarily imply clinical healing. Arkin's patient died four years later from cardiac and renal failure. Jager's patient also revealed the clinical evidence of a juvenile arteriosclerosis. Spiro's (8) patient revealed aneurismal formation, cicatricial healing, and healed infarcts in various organs, but death occurred from hemorrhage arising from multiple intestinal ulcers, due to infarct formation. On the other hand, there are a number of reports of apparent clinical recovery, although in none was the period of observation over four years. [Carling-Braxton-Hicks (9), (2 years)], [Harris, Lynch and O'Hare (10), (4 years)], [Grant (11), (3 cases, three years, three years and one year respectively)]. Spiegel (12) quotes a number of apparently healed cases, reported previously to those we have just quoted. Plaut (13) and others (12) describe typical lesions in the diseased and even in the normally appearing appendix, and occasionally in the female generative organs removed at operations for suspected disease. Klemperer (68) holds that a considerable number of such cases are not genuine instances of periarteritis nodosa because the vascular lesion is not a necrotizing one, but represents a hyaline or fibrinoid change. This may account for the fact that so many of such patients recover completely. Whether they will remain so time alone will decide. I recall a case later reported by Gross and Friedberg (14) in which death occurred months after the pathological diagnosis had been made from a removed appendix. Indeed the ultimate fate of the few apparently healed clinical cases would be most instructive.

The disease occurs predominantly in males and has been found in mammals [Joest and Harzer (15)].

*Etiology.* In recent years there has been a strong trend to view periarteritis nodosa as an allergic tissue reaction. This was first suggested by Gruber (16) in 1925 on two clinical grounds; first, the occasional history of previous allergic manifestations such as asthma (12, 17, 18, 11); and second, the very common history of a prodromal infection [Spiegel (12)]. Experimental verification of this suggestion has since arisen. Metz (19) in 1931 produced lesions identical to those of periarteritis nodosa by sensitization of animals with foreign serum and the streptococcus. Gerber (20) by means of repeated intravenously administered bacterial filtrates produced among other changes a necrotizing arteritis limited to the kidney with perivascular leucocytic infiltrative lesions which he believed represented a Schwartzman phenomenon. Masugi and Osibasi (21) obtained diffusely distributed lesions of periarteritis nodosa by sensitization with various bacterial strains. The anaphylactic nature of human periarteritis nodosa was first brought prominently into focus by Clark and Kaplan (22) who reported two cases of pneumococcus serum sickness in which typical lesions were found at autopsy. Later, Rich (23) reported periarteritis nodosa in five patients with serum sickness, and in one that received sulfathiazole alone. In one patient who recovered from the attack of serum sickness, hypertension and a slight diminution in renal function developed three months later. Subsequently Rich and Gregory (24) produced lesions in rabbits identical to those of periarteritis nodosa by sensitization with foreign serum. They regard these lesions as exaggerated expressions of the Arthus phenomenon, the histological structure of which was fully described by Gerlach (25) in 1923, who showed that in this phenomenon there is localized vascular necrosis with perivascular infiltration. Whether sulfathiazole produces the reaction directly or by way of sensitization will be later investigated by Rich and Gregory.

Rich and Gregory found these lesions fully developed after the seventh day of sensitization, thus confirming Fishberg's findings in his earliest reported human case. On the basis of their findings, they deem it important to determine and if possible to neutralize the responsible antibody in cases diagnosed during life.

These observations which seem highly convincing are significant not only because they are in accord with the clinical observations mentioned previously, but also because of the common coexistence of periarteritis nodosa with certain basic maladies whose genesis has also been ascribed to sensitization, namely, rheumatic fever and glomerulonephritis.

a. Rheumatic fever and periarteritis nodosa. There are a considerable number of reports of the association of periarteritis nodosa with rheumatic fever. The vast majority are invalid for purposes of proof, because the diagnosis is based on clinical data alone. In order to be decisive, it is essential to establish not only a clinical history of rheumatic fever but the characteristic rheumatic endocarditis and the presence of Aschoff bodies. With these criteria in mind, the report of Friedberg and Gross (14) is conclusive. Of a total of eight instances of periarteritis nodosa observed in the course of two years, they report four in which these criteria were fulfilled. In addition to these four cases, Friedberg and Gross report two that ran a febrile course with arthritis and clinical evi-

dences of glomerulonephritis and in whom at autopsy verrucous endocarditis but without Aschoff bodies were found. In view of this considerable percentage (50 per cent), the probability is strong that rheumatic fever and periarteritis nodosa are common associations. With less rigid criteria the number of reported cases of the association would be greater. One must remember that a larger number of reports antedated the discovery of the Aschoff body as the specific lesion of rheumatic fever, and furthermore, that no search for these bodies was made, or (what is more likely) the search was insufficient, because it sometimes requires a painstaking effort.

In a later report, Gross, Kugel and Epstein (3) report a necrotizing arteritis identical to that of periarteritis nodosa in the coronary vessels in 11 of 66 hearts affected by rheumatic fever. Four of these are included in their previous report, because the lesions were present throughout the vascular system. In the remaining seven the lesions were strictly limited to the coronary vessel. Whether periarteritis nodosa should be differentiated from "necrotizing arteritis" merely on the criterion of the local or generalized distribution is very doubtful. Klinger and Vaubel (26) in reporting the autopsy findings on their cases of rheumatic fever could not differentiate many of the lesions from periarteritis nodosa. They maintain that they are not different lesions but represent "varying responses to toxicity." They describe this evolution through the stages of granulation, hyalinization and fibrosis and eventually to scarring. Karsner and Bayless (27) in their study of the coronary arteries in rheumatic fever describe occasional lesions which may be interpreted as periarteritis nodosa. In 1923 Pappenheimer and von Glahn (28) reported rather characteristic findings in the larger vessels in rheumatic fever, previously observed by Klotz (29), characterized by dense scars in the vicinity of nutrient vessels both in the adventitia and in the media, often cellular. In two subsequent publications (30, 31) these observers described what seemed to be the earliest stage of these lesions. They found exudation of fibrin in and about the vessels, destructive changes in the cellular components of the vessel wall and around the vessel. These changes affected the vasa vasorum and many arterioles. They also noted the striking resemblance of these lesions to periarteritis nodosa. However, they differed from this lesion because of the absence of thrombosis and aneurysm formation, by the fact that the lesions affect vessels of lesser calibre and by the lesser degree of eosinophilic infiltration. Whether these represent entirely different reactions or are related, future studies must decide.

That the lesions of rheumatic fever may be due to hypersensitive reactions to bacterial products has been discussed repeatedly. One of the strongest advocates is Swift (32) who specially implicates the streptococcus, but the evidence has been only indirect, inasmuch as all attempts to reproduce the disease experimentally have been inconclusive.

In 1929, Gross, Loewe and Eliasoph (33) critically reviewed all previous experimental investigations to produce rheumatic fever and found none convincing. They attempted to reproduce the lesions and especially the Aschoff body by various methods and failed. Among the many recent attempts the most promis-

ing have been those of Vaubel (34) and Rich and Gregory (35). By repeated intravenous injections of large doses of horse serum into rabbits in steadily increasing doses, Vaubel and Rich and Gregory not only obtained typical lesions of periarteritis nodosa but also endocardial thickenings and what appear to be typical Aschoff bodies. Very recently (1943) Rich and Gregory have produced lesions in rabbits by sensitization with foreign sera that resemble human rheumatic lesions closely, including Aschoff bodies; they ascribe varying susceptibility to explain why certain rabbits develop lesions of periarteritis nodosa and others lesions of rheumatic fever. While Rich and Gregory do not claim to have settled the problem of the etiology of rheumatic fever, their findings are certainly provocative.

b. Glomerulonephritis and periarteritis nodosa. The coexistence of anatomical glomerulonephritis and periarteritis nodosa has been reported repeatedly (36, 37, 29, 38, 39, 12, 40). The probability is strong that when they do occur together they are simultaneous reactions.

The association of periarteritis nodosa with glomerulonephritis, as with rheumatic fever, is significant in the light of recent experimental investigations concerning the pathogenesis of glomerulonephritis. All attempts to produce the lesion of glomerulonephritis, identical to that in man, have hitherto been largely unconvincing. Masugi (41) in 1933 produced what appear to be typical lesions by nephrotoxins derived by anaphylaxis. Later he and Osibasi (21) reported identical lesions obtained by injecting bacterial antigens derived from the bacillus coli, streptococcus and the staphylococcus. Similar results with a wide variety of antigens have been reported by Rich and Gregory (35), Smadel (42), Smadel and Farr (43), Hemprich (44), Weiss (45) and Ehrich, Wolf and Bartol (46). As a matter of fact, priority for the discovery of this mechanism must be given to Longcope (47) who as far back as 1913 produced lesions very comparable to those in man by repeated injections of horse serum and egg white in dogs, cats, guinea pigs and rabbits. Clinical progression of experimental glomerulonephritis induced by a nephrotoxin with fatal issue has been shown to occur in rats by Smadel and Farr (43) and in rabbits by Hemprich (44).

Significant are the reports of Masugi and his coworkers (21, 48). Masugi and Sato produced both glomerulonephritis and periarteritis nodosa in animals sensitized to egg white by injecting the antigen both into the general circulation and directly into the renal vein. In the first series generalized periarteritic lesions were found. In the second, the most marked lesions were found in the renal vessels. Masugi and Isabasi (21) produced coexisting lesions of glomerulonephritis and periarteritis nodosa in three of eight rabbits sensitized with living and dead staphylococcus albus. Miura (49) likewise induced both lesions simultaneously by sensitization with foreign serum.

This association is significant because a necrotizing arteritis, particularly common in the afferent artery of the glomerulus, resembling that of periarteritis nodosa was noted in 10–20 per cent of autopsies in subacute and chronic glomerulonephritis (38). These lesions however differ from those of periarteritis nodosa by the absence of aneurysm formation, perivascular infiltration and

their localization to the afferent arterioles. The significance and genesis of this lesion will be discussed later.

The evidence therefore submitted is, to say the least, strongly indicative that anaphylaxis is an important agent in the development of glomerulonephritis. It accords with the clinical observation, that glomerulonephritis does not arise during the height of the infection, but after it has subsided.

*Relation of periarteritis nodosa to hypertension.* Hypertension is a common accompaniment of periarteritis nodosa. In 11 of the 17 cases of Spiegel (12) in whom the blood pressure was reported, it was elevated in 8; in most, appreciably so. Of the 101 cases collected by Harris, Lynch and O'Hare (10) 64 had hypertension. That in many instances, the lesion was primary and the hypertension secondary is evidenced in the progressive rise under observation. Most likely the hypertension is of the Goldblatt type due to progressive ischemia. In acute glomerulonephritis both the nephritis and the hypertension are evidently simultaneous reactions. In the chronic phase an increase in blood pressure may be superimposed by progression of the periarteritic lesion. Either with or without glomerulonephritis, the clinical syndrome of "malignant hypertension" may be induced. However, in the clinical syndrome known clinically as the "malignant phase of essential hypertension" (Fishberg) and anatomically, nephrosclerosis, the relationship to periarteritis nodosa is by no means clear. The association of the malignant phase of essential hypertension with periarteritis nodosa has been reported frequently (1, 50, 51, 11, 52). It is probable that in some of the reported cases the clinical picture of "malignant hypertension" was established before the sequence of these two lesions could be established, but on the other hand the clinical histories of many patients reveal that the essential hypertension upon which the malignant phase was superimposed long antedated the onset of the periarteritis nodosa. In this sense, the periarteritis must be a secondary phenomenon. This is particularly disturbing if one regards periarteritis nodosa as invariably the result of an anaphylactic mechanism. There is no evidence whatever in the histories of these patients of any disorder that indicates an allergic mechanism. Three possibilities arise: first, that either some other mechanism is at fault; second, that the lesion is not a true periarteritis nodosa but one that closely simulates it; third, that the characteristic lesions of periarteritis may represent a later phase of a pre-existing lesion. There are cogent reasons for believing that the last assumption is correct, and that the lesion supposedly pathognomonic of "malignant hypertension," namely arteriolonecrosis, represents the primary phase of periarteritis nodosa. We shall not discuss the nosological status of malignant hypertension and its counterpart in morbid anatomy, malignant sclerosis, except to say that it is not a disease in the sense that it has a consistent etiology, clinical course and anatomical background, but is a syndrome and more particularly a phase with a number of antecedent clinical and morphological backgrounds. In any event, the consistent lesion found in malignant hypertension is arteriolonecrosis, most commonly found in the afferent arterioles of the glomeruli and to a lesser degree in other viscera. Usually these foci of necrosis are accompanied by an accelerated and intense

arteriosclerosis. The one consistent clinical association is a high diastolic pressure and the issue now veers to a study of the relation between high diastolic pressure and arteriolonecrosis.

Some light has been thrown by the recent experiments of Wilson and Pickering (53) and Goldblatt (54) who found arteriolonecrosis in animals subject to prolonged and high intravascular pressure by the Goldblatt method with unilateral nephrectomy. (Neither of these observers measured the diastolic pressure.) Both these observers found the lesions widespread. Wilson and Pickering found a correlation in incidence between the height of the pressure and the lesion, but not necessarily to the duration of the hypertension. Goldblatt found that both excessive pressure and renal insufficiency were necessary factors in their production. Neither observer found these lesions in the kidney, which is not surprising in view of the low blood pressure in the renal artery proximal to the clamp. Subsequently, Wilson and Byrom (55) by producing high and sustained pressures in rats by narrowing of the renal vessel obtained necrosis of arterioles of the opposite kidney. As corroborative evidence, we cite the observations of Parker and Weiss (56) who found occasional arteriolonecrosis in the pulmonary circulation in some instances of tight mitral stenosis in which an extreme grade of hypertension of the pulmonary circulation was obvious.

The arteriolar necrotic lesions in human malignant hypertension resemble those found in periarteritis nodosa both in morphology and in size of the vessels affected and in distribution, although as a rule they are not nearly so ubiquitous. The distinguishing feature is the absence of the characteristic perivascular infiltration. Nevertheless many observers report transitions from none to perivascular infiltrations so pronounced that they invariably describe them as "resembling closely periarteritis nodosa" (57, 58, 38, 59, 60, 61, 62). Such infiltrations are found without glomerulonephritis and with glomerulonephritis (59). Horn, Klemperer, and Otani report such perivascular infiltrations as infrequent and that they occurred in areas where inflammatory lesions were more prominent. Shapiro (62) actually describes "transitions from moderately extensive necroses and slight periarteriolar infiltration to more extensive necrosis and a well defined picture of periarteritis nodosa as a later stage of extensive necrosis."

The point may be raised that these were instances of "primary" periarteritis nodosa with secondary "malignant hypertension," but this is hardly valid because the periarteritic lesions were found only occasionally as compared to the far greater number of necrotic lesions; in "primary" periarteritis nodosa, the lesions are widespread.

That the arteriolonecrosis of "malignant" hypertension and periarteritis nodosa are genetically akin receives some corroboration from experimental observations in which excessive and prolonged hypertension are produced. Wilson and Pickering (53) using the Goldblatt technique showed illustrations of lesions indistinguishable from those of periarteritis nodosa. Cromartie (63), by the Goldblatt technique produced typical lesions in rats between 6 and 12 months old. These were never normally present in rats less than 500 days old. Selye and Pavitz (64) also obtained typical periarteritic lesions in rats using desoxy-

corticosterone acetate combined with unilateral nephrectomy to produce excessive hypertension. The kidney showed the changes usually found in malignant nephrosclerosis. Goldblatt (54) in his earliest report on the vascular changes following the production of sustained and high intravascular pressure values found perivascular infiltration with polymorphonuclear leucocytes and lymphocytes in one case, but he ascribed these lesions as the result of a "probable coincidental infection." The precise mechanism whereby arteriolonecrosis is produced in both clinical and experimental malignant hypertension is not entirely clear. Although in experimental animals, renal insufficiency in addition to high intravascular pressures is an essential part of the mechanism, according to Goldblatt (54) clinically, periarteritis nodosa is by no means uncommon in the absence of renal insufficiency (38). Does the high diastolic pressure interfere with the nutrition of the vessel wall, or is a substance produced that acts as a necrotizing agent? (65). It is reasonable to assume that the perivascular infiltration with polymorphonuclears arises by chemotaxis. Most necrotic foci, whether intra- or extravascular, or whether they are infectious in origin or not, eventually become surrounded by such infiltrations. In the later stages the perivascular infiltration becomes granulomatous, histiocytes are predominant, and eventually fibrosis with its sequelae ensue. This as we have pointed out is precisely the sequence of events that occurs in classical instances of periarteritis nodosa. This mechanism would also account for the occasional occurrence of the lesions resembling periarteritis nodosa in other vascular lesions that are attended by necrosis, for instance in lupus erythematosus (66) and in the type of non-bacterial thrombotic endocarditis associated with fever, arthritis and serositis reported by Friedberg, Gross and Wallach (67). In other words, there is sufficient evidence that leads us to believe that the primary lesion is the necrosis, and the perivascular lesion is secondary. The relationship between arteriolonecrosis and periarteritis nodosa is essentially a quantitative rather than a qualitative one. Why the perivascular inflammatory reaction varies so in intensity depends, in all probability, upon the nature and intensity of the primary insult and the varying tissue reactivity of the individual's tissues. The morphological variations encountered depend upon the phase of its biological progression, and to a large extent the clinical expression is modified by the same token.

When one removes the three most common backgrounds of periarteritis nodosa, namely glomerulonephritis, rheumatic fever and the syndrome of "malignant" hypertension, only a small moiety remains in which the periarteritis is the sole incriminating lesion. Even in this fraction, periarteritis is a secondary event or a complication, and bears the same relation to the basic disease as, for instance, pleuritis to pneumonia. Nevertheless it deserves clinical recognition, in order to study methods to counteract or neutralize the primary mechanism. The possibility of healing rests on its recognition in its early stages.

*Clinical aspects.* The clinical aspects of periarteritis nodosa are the resultant of three large clinical backgrounds, rheumatic fever, glomerulonephritis and "malignant" hypertension plus the consequences of the widespread lesions, affecting the circulation and function of many organs. Periarteritis nodosa

therefore gives rise to a host of clinical expressions, depending on the degree and extent of functional impairment. For this reason, various "types" have been formulated, the cardiac, renal, gastro-intestinal, pulmonary, central nervous systemic, cutaneous, polyserositic, etc. (12). It is obvious that there is nearly always an overlapping, so that these types are usually combined. Why one organ is more involved than another is entirely speculative. It is not surprising therefore that the antemortem diagnosis of periarteritis nodosa is only infrequently made. In our experience, the more important diagnostic criteria depend on; first, an awareness of the possibility of such a diagnosis, second, the recognition of the multiple visceral involvement, especially with bizarre combinations, such as peripheral neuritis or fever, and third, evidences of predominant vascular disease, such as hypertension and hemorrhages into or from various viscera especially the kidney, intestine, skin and retina.

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CHAPTER 5

# LIBMAN-SACKS DISEASE

This malady which has a long life cycle, lends itself well to a discussion from the dynamic viewpoint because it is compounded of a wide variety of clinical phenomena ranging from a larval or primitive type to a more or less complete form, between which various symptom complexes arise that have been viewed as separate disease entities. Death by no means awaits the completion of the clinical picture; inasmuch as the disease may be latent for years, death may occur at what appears to be a larval stage. The disease is so widespread throughout the human frame and the clinical expression is so protean that even in its incomplete form, accurate recognition as a rule, is possible. While the specific morphological background, the indeterminate verrucous endocarditis, is often missing and while there is sometimes difficulty in correlating clinical with morphological data and vice versa, nevertheless, taken together, these data represent an entity so sharply circumscribed as to justify this eponym as a distinct disease, even before the unknown cause is discovered.

*The early or larval clinical evidences of Libman-Sacks disease.* This malady is remarkably sex linked. According to Baehr (1) males are affected in only 5 per cent of all cases. The predominant age occurrence is between the 11th and 40th years. It is most common in the third decade. In the report of Klemperer, Pollack and Baehr (2), 20 cases were all females. The youngest patient was 7 years old; the oldest 40. The disease is insidious and varies widely in respect to the earliest clinical evidence.

A. *Polyarthritis.* This was the first symptom in 9 cases. Frequently, there is a history of pains in multiple joints dating for months or even years before debilitating symptoms arise; in one instance 11 years. It cannot always be determined whether fever accompanied these attacks; under any circumstances, the diagnosis of "rheumatic fever" is often entertained. As a matter of fact, this diagnosis in some instances may very well be justified, because in a fair proportion of cases of Libman-Sacks disease that come to autopsy, rheumatic verrucous endocardial lesions are associated. This occurred in 5 of 23 hearts in Libman-Sacks disease examined by Gross (3). No joint or group of joints appear specially predisposed; the involvement is general. There are very few patients that escape polyarthritis some time in the course of the disease.

Indeed so frequent is the onset of Libman-Sacks disease heralded by what appears to be an "infectious arthritis", that the possibility of Libman-Sacks disease must be kept in mind, especially if it occurs in a young woman in whom no cause for the infectious arthritis can be discovered. Other clinical evidences of Libman-Sacks disease should be sought for, such as glandular enlargement, albuminaria, an unexplained patch of erythema, etc. Such circumspection has at times permitted an early diagnosis.

In one case that I recall the diagnosis of Felty's syndrome was considered because of an associated anemia, leucopenia and a palpable spleen. Later, the patient developed typical evidences of Libman-Sacks disease. More often, the polyarthritis is acute or subacute and is accompanied by fever. There is often a history of a number of such exacerbations before evidences of other visceral involvement set in, with prolonged intervals of remission, during which the patient feels practically well. I recall such a patient a young woman in her twenties, who was treated with gold. At the end of a few doses a violent high fever arose accompanied by an exacerbation of the polyarthritis and a generalized erythema multiforme which had the conformation of a butterfly lesion on the face. The gold was stopped and at the end of two weeks the fever and the erythema completely disappeared. A year later she died in another hospital of typical Libman-Sacks disease.

In contradistinction to rheumatic fever, the arthritis, according to some writers, leads to deformity if the disease is sufficiently prolonged (4). Baehr (37) has not observed this eventuality. Usually, the malady is not sufficiently prolonged to lead to such a result.

In summary, Libman-Sacks disease masquerades at times as a polyarthritis, acute, subacute, chronic or remittent, with or without deformity. Gyorgy (5) suggests that Still's disease in children may sometimes represent an incomplete manifestation of Libman-Sacks disease. This suggestion is founded upon the close clinical similarity between the two diseases. According to McCune (6) Still's disease is characterized, in addition to polyarthritis, by fever, glandular enlargement, secondary anemia, cutaneous manifestations and occasionally albuminuria. An additional similarity is evidenced in the frequency of an associated pericarditis; furthermore, according to Dawson (7) Still's disease is twice as common in females as in males. The possibility of such a mutation is suggested by the case report of Bayles (8) of a girl aged 12 who was diagnosed as Still's disease and who at post-mortem showed a non-constricting adherent pericardium without endocardial lesions and without Aschoff bodies. Unfortunately, the morphological findings in other organs are not reported. Inasmuch as there is doubt whether Still's disease is a disease entity or only a manifestation of rheumatoid arthritis in children, it seemed pertinent to investigate whether some cases of the adult type could be regarded as mutations of the Libman-Sacks disease, especially as pericardial and endocardial lesions have been reported as frequently associated in rheumatoid arthritis. Available data furnishes only suggestive evidence. Baggenstoss and Rosenberg (9) reported the high incidence of 56 per cent "rheumatic" lesions in 25 cases of rheumatoid arthritis. In

all but 2 Aschoff bodies were found. The pericardium was affected in 5 instances, in 2 with associated rheumatic endocarditis. In three it was the only structure involved, in one with a fibrinous, in the second with a fibrinopurulent exudate, and in the third the pericardial cavity was completely obliterated. Regrettably, the presence or absence of Aschoff bodies was not noted in the cases in which the pericarditis was the isolated lesion, nor are the case histories given or the histological findings in other organs. Bayles (8) found 6 rheumatic endocarditides in 23 cases of rheumatoid arthritis. In two others an isolated non-constricting healed adherent pericardium was present, without Aschoff bodies. One we have already quoted as having been diagnosed as Still's disease. The second, was in a woman aged 72 who gave no history of rheumatic fever; other data are lacking. As in Still's disease, there are certain parellelisms between adult rheumatoid arthritis and Libman-Sacks disease. Dawson (7) states that rheumatoid arthritis occurs three times as often in females as in males and almost always during the child bearing years. Enlarged glands occur in 53 per cent of all cases, there is a secondary anemia, and the incidence of pericarditis and adherent pericardium is 7 per cent. Pleuritis is common. Morphologically, Dawson finds vascular lesions with fibrinoid swelling, and fibrinoid changes throughout the ground substance of the mesenchyme, changes which have a striking similarity to those found in lupus erythematosus by Baehr, Klemperer and Pollack.

The evidence we have submitted is significant and suggests that there may be a common factor in both Libman-Sacks disease and certain instances of rheumatoid arthritis. The facts are sufficient to warrant a more complete study.

B. *Lupus erythematosus* is the next most frequent early manifestation of Libman-Sacks disease. Although Kaposi in 1872 recognized that lupus erythematosus was not strictly speaking a local manifestation of the skin but a symptom of a disease with a widespread visceral involvement which often leads to death, this fact was not widely recognized until the publication of Libman-Sacks (10) in 1924. In Klemperer, Pollack and Baehr's series of 20 cases, lupus erythematosus was the earliest symptom in 5, in every instance in the disseminated form, but often preceded by the discoid type. For a while, it was problematical whether the discoid and disseminated form of lupus erythematosus were distinct entities, but inasmuch as the discoid type passes into the disseminated, and less frequently, vice versa, (11), the probability is strong that they are simply variants of one and the same process. Baehr (37) has not observed these transitions. Whether the discoid type eventually always passes into the disseminated type is not definitely known, because the life cycle of Libman-Sacks disease sometimes covers a period of many years. Reports of "cure" of the discoid type, even for a period of years after the onset, must be viewed with reserve. For instance, Stickney and Keith (12) report a case in a woman who died at the age of 35 of Libman-Sacks disease. When she was 23 she had a discoid type of lupus erythematosus which remained healed for 11 years after therapy with quinine. At the age of 34 the eruption returned (after a sunburn) in a disseminated form; one year later she died. Not infrequently there is a history of recur-

rence of the discoid lesion with periods of remission. Case 4 of Klemperer, Pollack and Baehr's series showed a discoid lesion 9 years previously; it disappeared spontaneously but returned during the following 3 summers after exposure to the sun. Gold therapy was repeated after each recurrence. The year before she died, the rash reappeared in a disseminated form. Guion and Adams (13) report a patient in whom a typical butterfly rash appeared 9 years previously which reappeared each spring for the next 4 years, when it became disseminated. While generalized visceral involvement is usually associated with the disseminated form of lupus erythematosus, we have observed cases of discoid lupus in which evidence of visceral involvement are associated, for instance in the form of an albuminuria or general glandular involvement. Generalized Libman-Sacks disease with death may even ensue when the lupus remains discoid, as in the case of Edelman (14). Perhaps, this patient's severe thrombocytopenic purpura, a not infrequent complication of Libman-Sacks disease, caused death before the discoid lesion could become generalized. The very frequent history of the development of the rash after exposure to the sun may hopefully furnish the clue to the origin of the disease. Unfortunately, studies in this direction have proven inconclusive. Ludy and Carson (15) found hematoporphyrin in a large percentage of his cases of lupus erythematosus, which they ascribed to lead infiltration of the skin. Keil (16) also speculates on the possibility of lead poisoning as a factor, but the evidence, both for the hematoporphyrinuria and the indictment of plumbism is unconvincing. Attempts at treatment of Libman-Sacks disease by shielding patients from ultra violet light have not been satisfactory, perhaps because when hospitalized these patients are already in the advanced stages. In the past few years, we have found that patients with Libman-Sacks disease appear to develop a deeper and more lasting skin erythema after measured doses of ultra violet light than in controls. However, the method is still too crude and we hope to introduce a finer method shortly. This test may prove useful in early diagnosis, for instance in cases that present polyarthritis without other lesions. In one instance, this test proved of value.

The feature that has always puzzled students of Libman-Sacks disease is the occasional absence of either the discoid or disseminated forms of lupus erythematosus throughout the entire life cycle of the disease. This can be satisfactorily explained if we visualize lupus erythematosus not as the disease itself, but as a specific dermatologic reaction to an unknown agent. It is a facultative but not a necessary symptom of a generalized process, and would bear the same relation to Libman-Sacks disease as a specific rash in an infectious disease. In some infectious disease, the specific rash is sometimes absent, but this does not invalidate the diagnosis. Nevertheless the cause for the mutations, the remissions and the occasional absence of the lupus lesions in Libman-Sacks disease are entirely unclear. While sunlight often is the activating agent, one must assume a predisposition, the nature of which is a complete mystery. There is no evidence for assuming a constitutional factor unless one regards femaleness and the child bearing age period as parts of a constitution.

Lupus erythematosus is not the only lesion of the skin that the Libman-Sacks disease may present.

C. *Purpuric lesions* of various types are common. Libman and Sacks called attention to such lesions in their original paper. These purpuric lesions may be in the nature of white centred petechiae, which at once distinguishes Libman-Sacks disease from rheumatic fever, in which white centred petechiae never occur. These white centred petechiae appear to be directly correllated with the presence of indeterminate verrucous type of endocarditis. In exceptional instances, the white centred petechiae may arise from a complicating vegetative bacterial endocarditis. This occurred in 4 of the twenty cases reported by Klemperer, Pollack and Baehr. Another common form of purpura may simulate purpura hemorrhagica, the Henoch-Schoenlein purpura, or Frank's capillary toxicosis (17). In most such instances, the purpura is the result of thrombocytopenia, due to great reduction in blood platelets (18, 14, 19 20). This form of purpura may indeed be the first presenting sign of the Libman-Sacks disease. In one of Keil's 2 case reports a splenectomy was performed because of suspected purpura hemorrhagica; 10 months later, the patient developed a disseminated lupus erythematosus, ending in death. Finally, a lesion of the skin may arise that is identical with erythema multiforme, (21, 22, 23) and such instances have been classified under the heading of Osler's "erythema with visceral manifestations." Indeed Libman (24) in reviewing Osler's report of his 29 cases finds that two were probably cases of Libman-Sacks disease, since Osler refers to heart murmurs, rheumatic joint pains and a terminal nephritis.

Whether some of these various skin lesions are due to direct vascular damage is altogether probable. Klemperer, Pollack and Baehr describe collagen changes amounting in places to fibrinoid degeneration, which may affect the smaller vessels. In this connection, it is essential to speak of the lesions in the mucosa of the mouth that are frequent in Libman-Sacks disease. These are small, round or irregularly shaped shallow ulcers, often with dirty brown edges, situated on the palate or buccal mucosa, the tonsil or the tongue. They may be accompanied by small petechiae. They sometimes bleed. In association with other evidences of disease their presence may be of diagnostic significance.

Acute arthritis and the skin lesions therefore are by far the commonest initial signs of Libman-Sacks disease accounting for 14 of the 20 cases reported by Klemperer, Pollack and Baehr.

D. *Nephritis.* In two of the 20 cases the initial presenting symptom was nephritis as evidenced in one case by ankle edema, a marked albuminuria and hypertension, and in the second by the discovery of a profound albuminuria. When the rare opportunity comes to follow the course of the illness from the discoid lupus phase to the disseminated, one finds that albuminuria is a late development. In these two cases therefore, the disease must have been dormant for a considerable period. In the later phases of Libman-Sacks disease, albuminuria occurs almost uniformly. Albuminuria and expecially its precursor, microscopic hematuria, may serve as a diagnostic aid in the presence of other suggestive signs of Libman-Sacks disease; and is particularly significant if hyper-

tension is absent, for hypertension is exceptional in Libman-Sacks disease. The hematuria and albuminuria can usually be correllated to renal vascular alterations. This will be discussed later. Exceptionally there is a true glomerulonephritis. This occurred in 2 of the 20 cases reported by Klemperer, Pollack and Baehr. The albuminuria is usually accompanied by a renal insufficiency of moderate grade, the blood urea rarely approaching uremic levels. Hypoproteinemia is not unusual and may give rise to anasarca.

E. *Fever.* In one patient fever was the presenting symptom. Fever is the most consistent sign in the terminal phases of Libman-Sacks disease, and was present in 100 per cent of Klemperer, Pollack and Baehr's series. The fever may be unassociated with visceral changes but usually it accompanies either polyarthritis, serositis or pneumonia. There is a tendency to remissions with the subsidence of these evidences. In the terminal phases, the fever is continuous, sometimes attains excessive heights without causing profound subjective disturbance and the curve is completely irregular.

F. *Raynaud's syndrome.* The onset of the disease was ushered in in one of the 20 patients by this syndrome which persisted two years and was then followed by a butterfly rash and arthritis. I observed many years ago a Raynaud's syndrome in a male patient with disseminated lupus erythematosus who was discharged from the hospital and whose fate is unknown. One of the patients reported by Guion and Adams (13) presented the same symptom. Raynaud's syndrome in Libman-Sacks disease is attributable to the vascular lesions.

In the 20th patient, the early history was that of a cough with pain in the chest and fever of some years standing. The cough increased in intensity eight months before admission. This was followed by chest pain and a rash on the neck which followed exposure to the sun. She died five days after admission to the hospital and at post-mortem a bronchiectasis and pneumonia were found, and both the atypical verrucous and rheumatic endocarditis. Inasmuch as the previous data are insufficient to determine the sequence of events, one cannot decide whether the bronchiectasis was independent or followed the pneumonia. This patient was evidently almost moribund when she became hospitalized. We shall discuss the pulmonary complications of Libman-Sacks disease in a subsequent part of this communication.

In this review of the beginnings of the Libman-Sacks disease, we have covered the natural history of an appreciable proportion of the clinical expression of the disease. There are however other phenomena that may occur in various phases of the malady.

G. *Enlargement of the spleen* is only exceptionally sufficient to render it palpable. In only 3 of the 20 cases was the weight more than 300 grams. The most characteristic morbid change is a peculiar periarterial fibrosis limited to the central and peniciliary arteries. This was present in 19 of the 20 cases. Klemperer, Pollack and Baehr regard this lesion as almost specific for Libman-Sacks disease because they did not find it in a diversified control series. Kaiser (25) found this lesion in 15 of his 18 cases, and in a control series found the same lesion in a less pronounced form in only 3.2 per cent. Significantly, he found the

same lesion in four cases of thrombocytopenic purpura. In view of the fact, as we have shown, that thrombocytopenic purpura may be the earliest evidence of lupus erythematosus a follow up of these four cases might prove fruitful. Despite the apparent non-specificity of these perivascular fibrotic lesions, the high incidence in Libman-Sacks disease may be of pathologic diagnostic importance in cases that reveal a paucity of other lesions.

H. *Lymph node* enlargement was present in 9 of the 20 cases. While such enlargement may be manifest in the earliest phases, it is not sufficiently pronounced to warrant attention on the part of the patient. Enlargement of the lymph nodes is usually first noted in the cervical region (26). Morphologically there is distortion of the lymphoid architecture, edema, swelling of the lymph sinuses, hyperplasia of the endothelial cells, occasionally areas of necrosis and collagen changes such as are found in other organs. The areas of necrosis have been mistaken for tubercles. Fox and Rosahn also occasionally noted a perivascular fibrosis comparable to that found in the spleen.

I. *Myositis and dermatomyositis.* Painful muscles of the extremities occasionally with atrophy that is not due to peripheral neuritis are common in intermediary or advanced phases. In 5 cases Klemperer, Pollack and Baehr found moderate perivascular infiltration. In a sixth case there was intense interstitial and perivascular infiltration associated with myolysis of the psoas and rectus muscles. Keil (27) reports five cases in which he noted transitions of the lupus lesions to sclerodermatous-like thickening of the skin with pigmentation. In each instance there was a coexisting myositis. In some a biopsy showed edema of the muscle fibres with loss of striae, fibrous and perivascular leucocytic infiltration. He ascribes the lesions to vascular disease. Inasmuch as dermatomyositis is only a symptom complex the result of a number of mechanisms, Keil's observations show that lupus erythematosus may be one of the backgrounds.

J. *Ocular findings.* Retinal exudates, hemorrhages, papilledema or a postneuritic atrophy are among the ophthalmoscopic findings seen in Libman-Sacks disease. Either one or the other or combinations are usually seen in the late phases. The only report of the histology of the retinal changes is that of Goldstein and Wexler (28) who found atrophy of the walls of the retinal vessels with replacement by hyalin, and occasionally perivascular fibrosis. The ophthalmoscopic picture, which is by no means uncommon in Libman-Sacks disease, closely resembles that found in the malignant phase of hyperstension. Inasmuch as hypertension is exceptional in Libman-Sacks disease, such findings are of crucial diagnostic value in suspected cases.

K. *Central nervous system.* Libman (24) calls attention to peculiar convulsive seizures that occur in the late stages, in one of which the patient may die. In addition stupor and sometimes palsies may occur. The causes for these symptoms is not known, because little is known of the morbid anatomy of the cerebrospinal nervous system in this disease.

L. *The blood.* We have already referred to the thrombocytopenia. In addition there is nearly always a secondary anemia and a leucopenia. Blood

cultures are always negative, unless there is a superimposed infection. This will be discussed more fully in a subsequent part of this paper.

M. *Serositis.* A pleurisy with or without effusion may occur in the early stages, but usually it accompanies the intermediate and terminal phases. It may be recurrent with periods of remission. Usually pleural involvement is accompanied by fever. A pleuritis may be independent or may accompany pulmonary involvement. The latter event is often terminal. Morphologically, the pleuritis reveals nothing distinctive.

N. These remarks apply as well to the *pericarditis*, except in the fact that effusion is less frequently seen. The presence of a pericarditis is highly significant diagnostically and should be sought for in a doubtful case. Very often its presence establishes the diagnosis. It is especially important in the differentiation of Libman-Sacks disease from subacute bacterial endocarditis, in which a pericarditis is exceptionally rare (Libman, 24). A pleuritis and pericarditis frequently coexist.

Peritoneal involvement occurs but is rare. It probably accounts in part for the abdominal pains that occasionally occur in every phase of the disease, and occasionally for ascites.

N. *Pulmonary involvement.* Consolidation of the lung, usually bronchial or lobular in type, manifests itself at some time or other, sometimes early, but usually late. In the 20 cases reported by Klemperer, Pollack and Baehr, it was absent but twice. As we have already remarked, pneumonia is usually associated with a pleurisy with effusion. The pneumonia tends to migrate and may disappear and reappear a number of times before its lethal manifestation. Histologically, the pneumonic process is in no way distinctive (2).

O. *The heart exclusive of the pericardium.* Clinically, signs referable to the heart may be entirely absent throughout the course. Usually such signs arise in the intermediate or late phases. Tachycardia of considerable degree is the rule and is always noted terminally. Systolic murmurs may arise which cannot always be correlated with endocardial involvement, and contrariwise an endocarditis may be present without giving rise to a murmur. Gallop rhythm is common and usually a late event. Enlargement of the heart, if present, is usually moderate. The electrocardiogram shows no consistent pattern; the most common findings are low voltages and occasionally a prolonged P-R interval.

The main interest in Libman-Sacks disease centers around the endocardial involvement, which when present, is pathognomonic for this disease. In their original communication Libman and Sacks (10) emphasized the distinctive type of endocarditis at the expense of the clinical aspects, whereas, as a matter of fact, their clinical description of the disease which is remarkably complete, has since superseded the endocarditis in importance. Libman and Sacks employed the term "indeterminate verrucous endocarditis" since it had gross morphological characters distinguishable from the rheumatic and the bacterial varieties. Briefly, the vegetations are larger and flatter than those found in rheumatic fever and tend to spread for short distances along the valves or along the chordae tendinae. They appeared crinkled; the mural endocardium may be involved,

sometimes at a considerable distance from the valve; a favorite localization of the verrucae is in the angles between the flaps of the auriculoventricular valve and the mural endocardium. These were called "pocket lesions" by Gross. Histologically the most significant distinction from the lesions of rheumatic fever is the invariable absence of Aschoff bodies. The atypical verrucous endocarditis differs from bacterial endocarditis in a number of particulars. 1. Pericarditis is frequently associated with the indeterminate type but is excessively rare in bacterial endocarditis. 2. The vegetations are free from bacteria. 3. Blood cultures are invariably sterile. There are exceptions to these distinctions, both in respect to the rheumatic and to the bacterial type, as we shall discuss later. In their original communication, Libman and Sacks report four cases in which a full clinical picture of the disease which we have set forth is described, but they imply a distinction between the two cases in which a typical lupus erythematosus was present, and the remaining two in which it was absent. Strangely enough even in their report of these latter two cases, they described erythematous lesions on the extremities, one with purpura, which in the light of our present knowledge might have been regarded as true lupus erythematosus. This type of endocarditis is found in 30 per cent of all cases of disseminated lupus erythematosus. This figure applies only to the typical Libman-Sacks lesions. If one includes the cases previously described by Gross and Friedberg (29) Friedberg and Gross (30) and Friedberg, Gross and Wallach (31) as "non bacterial thrombotic endocarditis", with clinical histories closely resembling Libman-Sacks disease, some of which have since been shown (37) on further study to be genuine instances of the atypical verrucous endocarditis, the incidence would be higher. Furthermore, the percentage would again be raised if one included the early microscopic evidences of the beginnings of this type of endocarditis as described by Gross (32) and by Klemperer, Pollack and Baehr (2).

In their communication Libman and Sacks attempt to correlate this lesion not with the disease, but with the most striking sign of the disease, namely lupus erythematosus. This viewpoint has been perpetuated ever since, and has created confusion in regard to the proper nosology of the disease. As we have pointed out, lupus erythematosus need not be always regarded as an invariable accompaniment, nor have we the right to expect that it be so; even subacute bacterial endocarditis may pursue its course without petechiae, and scarlet fever may occur without a rash. Nor on the other hand have we a right to demand that the indeterminate type of endocarditis shall be an inevitable accompaniment of lupus erythematosus. A gross endocarditis does not always follow rheumatic fever. If one however, correlates the atypical verrucous endocarditis to the clinical picture, whether lupus is present or not, one is on surer ground, for I have not been able to find a single instance where an atypical verrucous endocarditis was found associated with some other type of malady than the one we have described. In other words, the lupus may be absent and the endocarditis may be absent, but the disease, whether complete or incomplete in its manifestations, is always present.

The Libman-Sacks disease cannot be defined with absolute certainty in all

cases by its clinical expression alone, because this is so often incomplete, but the diagnosis is absolute if the indeterminate verrucous endocarditis is found at post mortem. If this is absent and lupus erythematosus is absent, the clinical pathological diagnosis of Libman-Sacks disease can nevertheless be made with perfect assurance by finding one or the other of the visceral lesions that have been described so fully and accurately in the two contributions by Baehr, Klemperer and Schifrin (33) and by Klemperer, Pollack and Baehr (2). Viewing Libman-Sacks disease as a whole, the malady possesses well defined backgrounds clinically and anatomically and deserves a distinct place as a disease entity, and not as a syndrome.

The cardiovascular lesions in Libman-Sacks disease are further complicated by the not uncommon association with rheumatic endocarditis, bacterial endocarditis and the lesions of periarteritis nodosa. A rheumatic endocarditis was found in five of 23 hearts in Libman-Sacks disease, associated with the indeterminate type, which is a considerable percentage. Whether individuals with Libman-Sacks disease are more susceptible to rheumatic fever or vice versa awaits future study.

A bacterial vegetative endocarditis was found in four of the 20 cases reported by Klemperer, Pollack and Baehr. In one the staphylococcus was found in the blood culture; in the second a streptococcus hemolyticus; in the third, the streptococcus viridans, and in the fourth, an unidentified gram negative coccus. In one of three cases of Libman-Sacks disease reported by Keefer and Felty (34) a streptococcus viridans was found in a blood culture. In some instances, Klemperer, Pollack and Baehr could establish the fact that the bacterial infection was superimposed.

The lesions of periarteritis nodosa were found 3 times in the 20 cases reported by Klemperer, Pollack and Baehr. In a paper recently published, (35) I tried to show that periarteritis nodosa is not a disease but a reaction conditioned by fibrinoid necrosis of the vessel wall. This accounts for its occasional occurrences in glomerulonephritis, in rheumatic fever and in the malignant phase of nephrosclerosis. In these disorders as well as in Libman-Sacks disease fibrinoid necrosis of the finer vessels is common. As Libman (24) states, there is therefore no purpose in attempting to make a clinical differentiation between Libman-Sacks disease and periarteritis nodosa. One is a disease in the true sense of the word, the other is only a complication which may have a number of clinical backgrounds.

*Vascular lesions.* The vascular lesions in Libman-Sacks disease are so frequent, so generalized and so pronounced that originally Klemperer, Pollack and Baehr regarded the disease as essentially a vascular one. Inasmuch as vascular lesions are absent in a small percentage of all cases, Klemperer, Pollack and Baehr in a later publication (36) now regard the disease as an affection of the collagen which they view as a tissue system comparable to reticuloendothelial structures. According to Klemperer, Pollack and Baehr, the vascular lesions are fairly generalized but they are found most frequently and in a severe from in the kidney. There is a considerable variation in the intensity and extent of

the vascular damage not only in the individual case but in comparison of case with case. The vascular lesions represent stages. The first change is a deposit of fibrinoid material within the intima, between the muscle fibres of the media or within the adventitia. Further progression leads to involvement of more and more of the vessel wall, the result of fusion of the fibrinoid material within these layers. With complete fibrinoid change of the collagenous framework, destruction of the muscular and elastic elements ensues. Complete occlusion of the vessel occurs by massive swelling. Despite extensive necrosis thrombus formation within the wall is exceptional.

The capillaries partake in this vascular change. These also are most pronounced in the kidney and consist in the "wire loop" effect of the glomerular capillaries or focal necrosis of these capillaries. Klemperer, Pollack and Baehr regard the necrosis as the end stage of the wire loop effect. These capillary glomerular changes were found in 17 of the 20 cases. In other organs one sees changes analogous to the wire loop lesions in the presence of fibrinoid rings replacing the basement membranes of the capillaries.

*Is recovery possible?* This is a difficult question to answer because the life cycle of the disease is a long one and it would require at least more than a decade of observation before a case is pronounced "cured." There are a considerable number of reported cases (13, 26, 12, 2) in which a lupus erythematosus disappeared for a period of between five and eleven years only to return and end fatally. In view of the necrotic nature of the vascular lesions, the productive lesions in the endocardium, the serous cavities and the joints, one would at best expect a clinical healing but not an anatomical one.

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CHAPTER 6

# POLYCYTHEMIA VERA

In the final analysis the essential diagnostic differential between uncomplicated true polycythemia vera and secondary polycythemia due to hypertension of the pulmonary circuit or to prolonged mountain sickness, is the normal oxygen saturation of the blood (1). Nevertheless, Harrop and Heath (2) found that in polycythemia vera during exercise there is a lowered diffusion of oxygen. However, Barach and McAlpin (3) treated two patients by confining them in an atmosphere of 50 per cent oxygen for 15 and 17 days respectively without avail. This makes it very unlikely that anoxemia is a factor in the production of polycythemia vera.

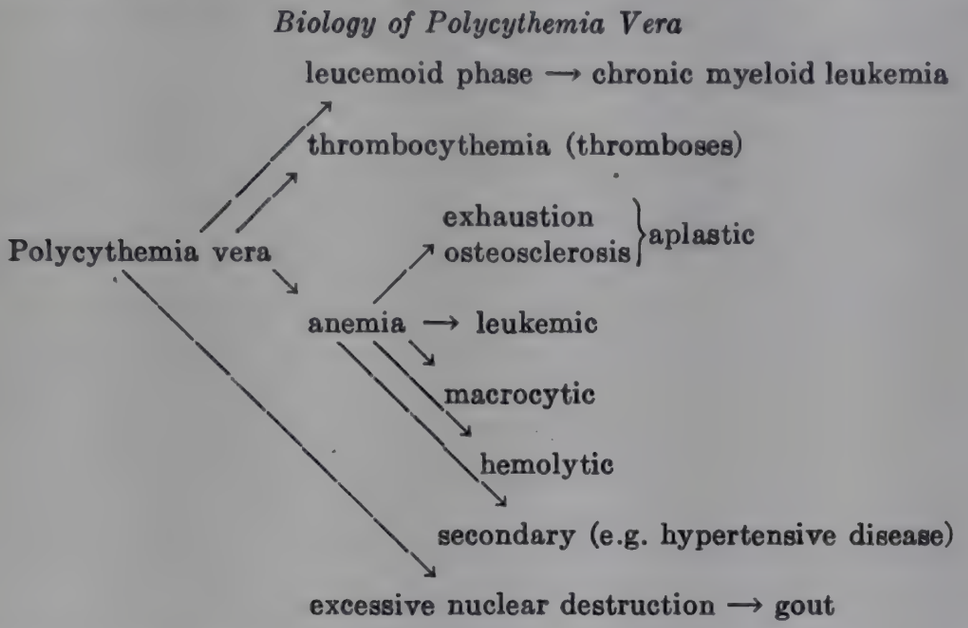
This explains the ruddy complexion of the patient with true polycythemia vera as opposed to the blue color of those afflicted with secondary polycythemia. It is generally believed that true polycythemia is distinguished from the secondary variety by the increase in the total blood volume. This distinction is not valid because I have observed on a number of occasions that if the blood volume is followed in patients with secondary polycythemia, it eventually increases often to degrees witnessed in true polycythemia. Apparently an increased blood volume is the final compensatory mechanism for the continued anoxia, comparable to the loss of concentrating ability and consequent polyuria observed in progressive renal insufficiency.

Being a disease of many years duration and of insidious onset, the opportunity to observe the entire life cycle of the malady is rare indeed. The earliest phase is practically unknown. Harrop (4) states that in the course of routine blood examinations in students, it is not unknown to find one or more students with a high erythrocyte count. In two instances studied by Harrop the spleen was definitely palpable. He quotes Lommel (5) who reports similar observations. Rosenthal and Bassen (6) also report asymptomatic cases that were discovered in the course of routine examination.

Under ordinary circumstances, the patient with true polycythemia pursues life for years with a fair degree of efficiency and free from complications. Occasionally, hypertension arises, an association that Gaisbock (7) tried to create as a separate disease entity, but it is now generally held that this association is a

mere coincidence, related to the age incidence. The only mechanism whereby true polycythemia may give rise to hypertension is the increased viscosity of blood but this would affect the blood pressure by a rise of but a few millimeters of mercury. Nevertheless, the cardiovascular-renal syndrome arising from essential hypertension is by no means an infrequent association. I have seen a number of such cases. In all phases of the disease, patients with polycythemia vera are subject to thromboses, both arterial and venous. [Oppenheimer (8), Brown and Griffen (9), Diedecke (10).] These are largely the result of the thrombocythemia, so commonly present in polycythemia vera (vide later). In part they may also be due to the high blood calcium which has been reported by some observers. (Brown and Griffen (97).)

Typical gout is by no means an infrequent complication of polycythemia vera. I have seen about three or four such cases. This complication has been reported by many observers, for instance by Reifenstein (11) and Weber (12). The




gout is probably the result of the extensive nuclear destruction consequent upon the excessive production of erythrocytes. This also explains the occasional high uric acid content of the blood (Isaacs (13), Shelburne and Hanzel (14), Erickson (15).)

*Transition of polycythemia vera to leukemia.* As a rule, there is a leucocytosis as well as an erythrocytosis in polycythemia vera, which usually is progressive, so that white blood counts of even 20 to 30000 per cu. m.m. are by no means uncommon. Also in most instances of long duration, myelocytes and other forms of immature leucocytes appear in the blood, corresponding to an increase in the leukoblastic elements in the bone marrow. Minot and Buchman (16). This phase of the disease is often referred to as the *leukemoid*. Eventually a blood picture typical of that of true leukemia may ensue. (Minot and Buchman (16), Rosenthal and Bassen (6), Reifenstein (11), Klump and Herzberg (17), Hedenius (18), Blumenthal (19), Prendergass and Pancoast (20), Herxheimer (21).) Furthermore, the blood picture does not merely represent an increased leukoblastic

activity of the bone marrow, but a true leukemia; this is shown by post-mortem studies in which true myeloid leukemic infiltration is found. (Minot and Buchman (16), Rosenthal and Bassen (6), Klump and Herzberg (17), Hedenius (18), Reifenstein (11). How frequent the transformation of polycythemia vera into leukemia occurs cannot be affirmed with any assurance because observations upon this disease are usually limited to only a small cross section of its life cycle, but that it is fairly common is indicated by the observations of Minot and Buchman (16) who report this transition in three out of fifteen cases. The cause of this transformation is as obscure as the cause of polycythemia vera and of leukemia. Some have suggested that the malady bears many of the earmarks of a malignant neoplasm.

*Transition of polycythemia vera to anemia.* I have observed a number of untreated cases of polycythemia that eventually developed anemia. A considerable number of observers have reported such transitions. The anemia is of various types. Thus Minot and Buchman (16) report three cases of secondary anemia with leukemic blood pictures, one showing the typical anatomical changes of leukemia at autopsy. This type of anemia accompanies most of the reported cases of transition from polycythemia vera to leukemia. A second type is the aplastic as reported by Rosenthal and Bassen (6), Freund (22) and Hirschfeld (23). In two of Rosenthal and Bassen's cases this type was accompanied by osteosclerosis of the bone marrow, similar to that observed by Hirsch (24). An anemia resembling hematologically macrocytic anemia has been reported by Delbouge, Gotschlick and Froboese (25) and others. Whether these are nosologically transitions to true pernicious anemia is very much open to question. There are a few reports of transitions to an anemia of the hemolytic type as indicated by an increased output of urobilin and an increased fragility of the erythrocytes. (Minot and Buchman (16), Weber (12), Mosse (26), Avery (27).) When hypertensive disease is associated, a secondary anemia may result when the hypertensive disease reaches its terminal nephritic phase.

The anemias following treatment by radiation, benzol or phenylhydrazine or repeated venesection obviously are not relevant in a discussion of the biology of polycythemia vera.

It is obvious that the cause of the anemia that is occasionally observed as a terminal event in polycythemia is various. Overstimulation of the bone marrow, a view expressed by Harrop (2) is a plausible explanation but may be regarded as only one of the factors.

*Transition of polycythemia vera to thrombocythemia.* A priori, one would expect that the third morphological component of the blood, namely the blood platelets, would occasionally partake in the general rise accompaying the erythrocytic and leukoblastic activity in the bone marrow and this, indeed, is found to be the case. An increase in the megakaryocytes in the bone marrow has been reported by numerous observers. Minot and Buckman (16), Hutchison and Miller (28), Askanazy (29), Weber (12) and Di Gugliemo (30) and Rosenthal and Bassen (6). Indeed, Minot and Buchman (16) have occasionally discovered them in the peripheral blood. Accompanying this increase in megakaryocytes,

there is a thrombocythemia. This transition must be common because Rosenthal and Bassen (6) in a wide experience found a thrombocythemia in 30 per cent of their cases. The relation between the thrombocythemia and thromboses has already been commented upon.

It is evident therefore, that polycythemia vera at any particular cross section of its clinical course does not necessarily imply that it is an end result. Its evolution is various, depending on incidental complications and the opportunity to observe the malady over a prolonged period. If one sees the disease in one of its terminal phases, for instance, the leukemic, it is sometimes difficult to reconstruct the previous clinical course. There are probably many cases of what appears to be a primary chronic myeloid leukemia that were originally cases of polycythemia vera.

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CHAPTER 7

# LEUKEMIA

Few diseases illustrate the need of a biological interpretation more than the leukemias. The conventional static study of these diseases has resulted in a bewildering classification and terminology, largely because phases have been demarcated as distinct disease entities. This is due in the largest measure to the insufficient realization that the cells of the hematopoietic system are endowed with potentialities for change in morphology and function that are not even necessarily synonymous with maturation. Indeed, such a change more often represents a reversion to an embryonic status. The issue has been further confused because the definition of certain disease mechanisms, such as "inflammation," "hyperplasia" and "neoplasia" has received a wide range of interpretations. Until these mechanisms are better understood, it would simplify matters considerably to depend upon observations of clinical and morphological transitions and to note their sequences and correlations. A study of very early cases is particularly desirable.

One of the consequences of the various interpretations has been the lack of a sharp definition as to what is meant by the term "leukemia." A clinical and morphological correlation is not always present. In other words, there may be a greater or lesser percentage of immature leucocytes in the blood without leukemic infiltrations in the organ and on the other hand, there may be the characteristic leukemic morphological changes (pseudoleukemia) without either an increase in the number or the presence of immature leucocytes in the blood (aleukemia). Nevertheless, the aleukemias very often later develop the characteristic hematological changes. This does not imply a change in the nature of the disease, but only a biological change. Furthermore, as the result of secondary changes in the hematopoietic organs, the true nature is often clinically masked by a superimposed clinical expression, such as granulocytopenia, hemolytic anemia, aplastic (myelopthisic) anemia, thrombocytopenic purpura, etc. and it is only by a study of the tissues, especially the bone marrow, that the true nature of the disease is disclosed. These clinical and morphological shifts render the diagnosis an occasionally difficult one, and it is only by a mutual study from both points of view and especially by the observation of transitions, both clinical and morphological, that the true nature of leukemia can be established. Even under such circumstances, the diagnosis is sometimes doubtful.

*Chronic lymphatic leukemia.* Being an insidious disease, the earliest phase in man is not known. The closest approach was a case reported by Stasney and Downey (1) which eventually developed into a subacute lymphatic leukemia. Three successive biopsies of lymph nodes were performed. In the early stage the node showed a "hyperplasia" of the reticulum cells. At the same time, the peripheral blood showed cells of the "reticulo-endothelial" type but with a nucleus of lymphocytic pattern. The later biopsy presented a dense mass of immature lymphocytes in the medullary region of the lymph node. The "reticulo-endothelial cells" disappeared from the blood and only immature lymphocytes were present. In their view, the case reveals the embryonic potency of the syncytial reticulum cells. If mouse leukemia is identical with human leukemia, the findings of Stasney and Downey are precisely duplicated by Potter, Victor and Ward (2) who found that the early phase of lymphatic leukemia in the mouse is a "hyperplasia" of the reticulum of the medullary tissue of the lymph nodes and the perivascular regions of the liver. These observations coupled by clinical experience already demonstrates that "aleukemic" leukemia is not a separate disease but represents a transition to the subleukemic and finally to the leukemic phase. As Opitz (3) observes, it depends upon how long the patient lives. It is true that many leukemic patients die even in the aleukemic stages, but in such death is often the result of factors unconnected with the fullest fruition of the disease.

The biology of chronic lymphatic leukemia is closely related to the potentialities of the lymphocytes and especially toward neoplasia. There has been much debate ever since Babes (4) broached this possibility and there are certain transitions that suggest such a neoplastic origin, from the point of view of aggressiveness, cell atypicism and metastatic invasion. We refer especially to the cases in which the earliest manifestation of the disease is a localized growth of the lymph nodes that has been termed "leukosarcoma" (Sternberg) "lymphosarcoma" (Kundrat), "lymphocytoma", "reticulum cell sarcoma" and "giant follicular lymphadenopathy." These, with or without leukemic infiltrations have been grouped under such terms as "lymphadenosis" or "lymphomatosis." The reports of a leukemic blood picture following such an event are common enough (5, 6, 7, 8, 9, 10, 11). The primary tumor may be in the mediastinium, intestinal tract, regional lymph nodes, skin, bone, etc. The question arises whether these cases represent true transitions of sarcoma into leukemia or a malady distinct from leukemia. The latter view is held by Richter (11) Isaacs (5) on morphological grounds, since the hematic cells in their cases were not true lymphocytes, but had the characteristics of "lymphosarcoma" cells. To their view, despite the presence of true "leukemic" infiltration in the liver and spleen, these represent cases of lymphosarcoma in which the neoplasm has broken into the blood vessels and has spread throughout the organs by colonization. In this interpretation, the "leukosarcoma" which has no distinctive morphology must be differentiated from the other forms of sarcoma previously mentioned. This interpretation however does not take into consideration the fact that the cell morphology is not absolute and true to type but relative, and

depends, as Klemperer (12) emphasizes, upon the potentialities of the cytoplasmic reticulum of the myeloid and lymphoid tissue, which, under various abnormal conditions, reverts to its embryonic functions. One of these functions is the development of cells along hematic lines and the type of cell will vary according to the degree of differentiation. This has been shown in the cells of fixed tissue. Banti (13), Klima (14) and Opitz (3) call attention to the frequently different morphology in the biopsy as compared to the autopsy in lymphatic leukemia. Ehrlich and Gerber (15) describe three dominant types of cells in lymphosarcoma —small lymphocytic, large lymphocytic and intermediate—but admit that they are usually mixed and that they display transitions from biopsy to autopsy. Nevertheless they believe that lymphosarcoma in their sense differs from the "lymphadenoses" in certain particulars, especially in their regional origin, in the tendency to metastatic deposits, and in the presence of leukemic cells in the blood stream. They also showed that the amount of fibrillar reticulum which is a derivation of the cells varied in specimens removed at different times. Klemperer (12) illustrates these transformations from specimens removed at different stages and he shows changes from a "lymphosarcoma" to a "reticulum celled" sarcoma and reversely. Even the giant follicular lymphoblastoma eventually transforms into either "lymphosarcoma" or "reticulum celled" sarcoma, and occasionally even into lymphatic leukemia (7, 8, 10). This potentiality of the fixed cytoplasmic lymphoid reticulum accounts for the varying interpretations of these types. In the last analysis they represent mutations and thus far the attempts to subdivide them up into well defined species has only confused the issue and has introduced a bewildering terminology. What factor or factors influence the change in one direction or the other are not entirely clear. One of the factors, as we shall point out shortly, is radiation.

This change applies not only to the fixed lymphoid reticulum but to the free cells that have entered the circulation. We have already referred to Stasney and Downey's observation that the hematogenous cells changed from a "reticuloendothelial" to pure lymphoid type in the later stages. Wiseman (9) reports normal lymphocytes mixed with "neoplastic" cells within the blood. Graetz (17) reports cases of leukosarcoma in which in the early phases small lymphocytes were the dominant blood cells, while in the terminal phases they were large.

The attempt to differentiate types of lymphatic leukemia from the morphological study of the cells of the lymphoid type in the blood alone must be viewed with reserve.

The problem now arises whether this type of lymphatic leukemia, which begins at a localized swelling of the lymphoid reticulum and after passing through an aleukemic phase into a leukemic, is a different disease than the conventional type which is presumed to begin in an autochtonous form with generalized lymph node swelling. The advocates of this dichotomy point to the different course, the different morphology of lymphoid cells both in the tissues and in the blood, the comparative absence of localized tumor formation and splenomegaly and lymphoadenopathy in the cases that begin with "leukosarcoma" and the infrequency of metastatic deposits in the conventional type of lymphatic leukemia.

On a critical appraisal it seems to us that these differences are more specious than real. In the first place, neither type is biologically pure since there is abundant evidence that more or less crossing of these differentials is extremely frequent; second, as we have tried to show, there is no sharp distinction in the morphology, since mutations are exceedingly common; third, the differences are based on the assumption that in the conventional type of leukemia the characteristics began as such and did not pass through a developmental stage. We have already cited the important observation of Stasney and Downey, that lymphatic leukemia begins from a small focus in the pulp cords of the medulla which spreads peripherally throughout the lymph node and that it passes from an aleukemic phase to the leukemic termination. This is precisely comparable to the type of leukemia which begins as a "leukosarcoma" except on a smaller scale. Furthermore, if experimental mouse lymphatic leukemia may be regarded as the analogue of that in man, the identity of the generalized lymphatic leukemia with the leukosarcomatous variety seems perfect. Furth, Siebold and Rathbone (18) found that after intravenous injection of certain strains of living leukemic cells they were able to obtain in all instances a lymphatic leukemia which was preceded by a transient aleukemic stage. By subcutaneous inoculation, they usually produced a leukosarcoma with metastases and in rare instances lymphatic leukemia without tumor formation. Furth and Kahn (19) could inoculate mice with leukemia with a single living cell. Furth and his coworkers conclude that lymphosarcoma, "leukosarcoma" aleukemic lymphomatosis, leukemic lymphomatosis (lymphatic leukemia) are identical and represent different manifestations of the same disease. Richter and Mac Dowell (20) and Webster (6) are of the same opinion. Certainly when both types have attained their fruition, they are both clinically and morphologically indistinguishable.

One of the factors that determine the transition from leukosarcoma to lymphatic leukemia is undoubedly x-ray therapy. This sequence has been noted by a number of observers (21, 22). Furth and his coworkers created a greater susceptibility in their animals by subjecting them previously to x-rays. This has been confirmed by others (21, 22). This no doubt accounts for the fact that the incidence of lymphatic leukemia in radiologists is ten times greater than in non-radiological physicians (23).

The biology of lymphatic leukemia, as we have outlined it, is paralleled in other types of leukemia. This will be discussed shortly.

There are other mutations in lymphatic leukemia that may complicate the clinical expression. It is sometimes difficult to determine whether these mutations are initial or terminal phenomena since the malady had already attained considerable progress before clinical manifestations arose. We refer to the various types of anemia and to the changes in the granulocytes and platelets that have been frequently noted in association with lymphatic leukemia. The anemia is usually normochromic and rarely hyperchromic. Although the blood picture of the hyperchromic variety simulates pernicious anemia and the combination has been termed "leukanemia," a valid pernicious anemia with complete achlorhydria has never been reported as associated with lymphatic leukemia. A

"leukanemia" is therefore not a separate entity. The anemia may be accompanied by a thrombocytopenia (9, 14, 24) or it may resemble the aplastic or myelophthisic type (9); exceptionally it may resemble a hemolytic anemia, which is sometimes the earliest manifestation (24, 25, 26, 27). When these mutations occur early the diagnosis may only be cleared by bone marrow puncture. We have observed a number of such instances. Lymphatic leukemia is sometimes associated with the clinical and morphological manifestations of a granulocytopenia (9, 24) and occasionally unripe granulocytes may appear in the blood (28). All these mutations are in some measure due to invasion of the bone marrow by the leukemic process. The presence of immature granulocytes in the blood may be accounted for by a compensating extramedullary hematopoiesis, comparable to that which occurs in cases of extensive osseous metastases. The various stimuli that set forth the remaining types of mutations are obscure. In how far x-ray therapy leads to these mutations has not been entirely clarified.

*Myeloid leukemia.* The earliest lesion of myeolid leukemia is entirely unknown, the reason being that it is an insidious disease and does not become clinically manifest until the lesions are fairly advanced. Although experimental myeloid leukemia with living leukemic cells in certain strains of mice (29, 30) and in fowl by a filterable virus (29) can be fairly consistently produced by the same procedure and with identical results as in experimental lymphatic leukemia, the earliest phases are not reported. It is possible that the cases of "aleukemic myelosis" (32) or "aleukemic reticulosis" (33) represent, if not the earliest, at least an early stage. That chronic myeloid leukemia may also pass through an aleukemic phase has been shown by King (34). Chronic myeloid leukemia does not follow the acute form since clinically, anatomically and hematologically they appear to be entirely different diseases. Since the potentialities for differentiation of the hematocytoblast (Ferrata) which is generally regarded as the progenitor of the myeloid series is greater, morphologically speaking, than that of the lymphoid reticulum, a wider range and atypicism of cells in both fixed tissue and in the blood are noted in myeloid leukemia than in lymphatic leukemia. Both tissues and blood contain a wide variety of cells of the myeloid series, from the unripe to the mature form, including eosinophiles and basophiles; and the longer the disease lasts the more immature the cell, so that eventually instead of myelocytes, the predominant cell type is the myeloblast. In acute myelogenous leukemia, on the other hand, the potentialities for differentiation are almost lost, since there are few or no intermediary forms between the myeloblasts of the blood and the mature segmented types. There is no conclusive evidence that lymphatic leukemia is converted into myeloid leukemia. We have already noted that cells of the myeloid group may pass into the blood from extramedullary hematopoiesis in lymphatic leukemia, but this does not constitute a transformation, nor is there any positive support for the transition of myeloid into lymphatic leukemia. Most of such reports date before the differentiation between lymphocytes and myeloblasts was rendered possible.

In other respects the evolution of myeloid leukemia parallels that of lymphatic leukemia closely. Tumors of the blastomatous type have been described, al-

though they are not nearly as frequent as in leukosarcoma. The most familiar are the chloromata arising from the bone or periosteum. These are always associated with acute myeloblastic leukemia. Cooke (35) reported nine cases of acute leukemia in children associated with a large mediastinal sarcomatous mass. In four, this mass preceded a rather sudden invasion of the blood with leukemic cells, despite the disappearance or lessening of the size of the mass by x-ray. Such mediastinal masses were present in two of forty-eight cases of myelogenous leukemia in adults reported by Kirklen and Hefke (36). Tumors of other parts of tissue associated with "myelosarcoma" have been reported by others (37, 38, 39). The blood invasion sometimes follows x-ray treatment, or without it.

Hematological mutations similar to those described in lymphatic leukemia have been described in myeloid leukemia. Hemolytic icterus has been reported by Brill (40), Boe (27) and Klima (14), thrombocytopenia and granulocytopenia by Klima and Seyfried (24) and Opitz (3). Sternal puncture again is decisive. The stimuli that cause these mutations is not definitely known. As in lymphatic leukemia, radiation may be a factor.

*The transition of polycythemia vera to myeloid leukemia.* The term "erythroleukemia" which has been applied to the association of true polychthemia with leukemia does not deserve a demarcation as a separate disease entity, since opportunities to observe over prolonged periods have shown that the leukemic element always represents a transition from the polycythemic phase (41). The cases that have been reported of a transition in the reverse direction are of doubtful validity (42). It may require many years to observe the transition from a leucamoid reaction in the blood to the terminal classical clinical and morphological characteristics of a myeloid leukemia (41). As far as we are aware, no instance of a transition to lymphatic leukemia has been reported. It is of course possible for a lymphatic leukemia to be associated with a polycythemia, due for instance to obstruction of the superior vena cava by a mediastinal leukosarcoma, but in such instances, the polycythemia is compensatory and secondary as proven by a lowered oxygen saturation of the blood. In uncomplicated polycythemia vera, the oxygen saturation is normal. Whether all individuals with polycythemia vera would ultimately transform into a myeloid leukemia, provided they did not die from intercurrent disease, or whether an additional factor stimulates this transition, it is of course impossible to say. In view of the lowered resistance to leukemic invasion in experimental animals by x-ray and the extraordinary frequency with which leukemia develops in "leukosarcoma" following similar treatment, it is probable that this factor acts as a stimulus (43, 44).

*The transition of myeloma (plasmocytoma) into plasma cell leukemia.* Although myeloma is usually limited to the bone marrow, extraosseous growth, especially of the lymphatic structures, have been reported and when these represent the original manifestations of the disease, the diagnosis of plasmocytoma is made. It is questionable whether "plasmocytoma" represents a separate entity, as some aver, or not. Jackson (45) and his coworkers do not believe so and regard both myeloma and extramedullary plasmacytoma as different manifestations of a

generalized neoplastic disorder of the lymphatic system. The matter of classification of plasmacytoma and myeloma is confused by the fact that the plasma cell and the myeloma cell resemble each other so closely, and what appear to be typical instances of myeloma, are reported as of the plasma-celled type and reversely. Whether such a distinction is valid is questionable, because both are derived from the same parent cell, the lymphoid type. There are undoubted plasmocytomata that are extraosseous and remain extraosseous. These have been recently reviewed by Hellwig (46). The extramedullary myelomatous invasion of parenchymatous organs, for instance the liver, spleen and kidneys, associated with an unusual invasion of the circulating blood with plasma cells creates a variant that has been termed "plasma cell leukemia." Most of the reported cases of plasma cell leukemia are associated with myeloma of the bone, Bence-Jones proteinuria, and hyperproteinemia, and many are accompanied by plasma or myeloid infiltration of the parenchymatous organs. Piney and Riach (47) divide myeloma into the leukemic and aleukemic types. Rubinstein (48) postulates that myeloma bears the same relation to plasma cell leukemia as lymphosarcoma to lymphatic leukemia. In one of his cases there were 60,000 cells of which 65 per cent were plasma cells. In another there were 23,000 cells with 16 per cent plasma cells and 8 per cent myelocytes. Patek and Castle (49) report a case with 50,000 leucocytes of which 33 per cent were plasma cells. Most of such reports represent counts made in the terminal phases. When counts are made serially from the early to the terminal phases, there is as a rule, a progressive rise both in number and percentage of the young forms. Thus Rubinstein reports a rise in the total white blood cell count from 6,000 to 26,000 and a percentage increase of plasma cells from 0.5 to 38 per cent. However, plasma cells may never appear in the blood at any stage, even when there is a pronounced myeloid invasion of the parenchymatous organs as in the case of Churg and Gordon (50).

*Monocytic leukemia.* The precise status of monocytic leukemia within the rubric of the leukemias is still debated, although its behavior is precisely like that of established forms of leukemia, both clinically and in respect to aleukemic state (51, 52, 53, 54), its association with tumor formation (51, 55, 52, 54), and the hematological mutations (52, 56, 57). One of the difficulties as Forkner (52) says, lies in the different interpretation of its origin; whether it comes from the lymphocytes, the primitive mesenchymal cells (58), the endothelium, or the reticuloendothelium. With the supravital and peroxidase stain technique, Sabin, Doan and Forkner (58) proved to their satisfaction that the monocyte is a specific cell. However this has not been substantiated by others (59, 60, 61). It seems to us that it is not a question whether the monocyte is a specific cell of a precise origin, but whether it represents a phase in the maturation of the cells of primordial cytoplasmic reticulum which includes all the above mentioned tissues. It is not the specificity of the cell but the dominance of the type that determines the present day classification of the monocytic leukemias. As a matter of fact other unripe cells other than the monocytes have been frequently noted in the blood, especially cells of the myeloid series (51, 62). Doan (57)

followed a case of myelocytic leukemia for twelve months and at one time there appeared a shower of monocytes in the blood so that they comprised a large per cent of the total white cells in the blood. Mitchell (54) also reports such a change, which he believed followed x-ray therapy. On the other hand, Kracke (59) and Ederle and Esch (56) have noted a number of monocytic leukemias that terminated in a definite myeloid leukemia. The factors that determine the predominance of the monocyte at some phase or the other in the course of the malady is again unknown, and will probably remain so until the cause of leukemia is discovered. In all likelihood, therefore, monocytic leukemia represents a phase of myeloid leukemia.

Monocytic leukemia is often associated with what is termed a "reticulosis." It is difficult to appraise what is meant by this lesion, since the interpretations are so diverse. It is sometimes referred to as a "hyperplasia" and sometimes as a "neoplasia" with potentialities toward the development of reticulum celled sarcoma or lymphosarcoma (63). Some regard reticulosis as originating in the reticuloendothelial system, and therefore the cells that enter the blood stream are "reticuloendothelial" in type. Others regard "reticulosis" as "hemocytoblastosis" and therefore belongs to the aleukemic or leukemic histioblastoses (12). As a matter of fact, all these various transitions have been reported, with neoplasms and without neoplasms, with leukemia and without leukemia and in various sequences.

It would appear that if cell specificity is ruled out as the criterion in the interpretation of leukemia and a biological approach is made based upon the potentialities for differentiation of the cytoplasmic reticulum of the myeloid and lymphoid tissue, it will bring unity to a much confused subject. In addition one needs as Richter (64) insists, a better understanding of the process termed "hyperplasia" and "neoplasia."

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CHAPTER 8

# FOLLICULAR LYMPHOBLASTOMA

In 1925, Brill, Baehr and Rosenthal (1) described a disease with clinical and morphological characters that warranted a separate classification in the broad group of lymphomata. In a number of papers since then Baehr and his associates have amplified this concept and, what is of special significance, have observed a sufficiently large series of cases of follicular Lymphoblastoma to enable them to study their end results.

For the following exposition of the clinical and morphological characteristics of the disease, I am indebted to the latest publication of Baehr and Klemperer (2).

In the earliest stages, the disease is asymptomatic except for a generalized painless enlargement of the lymph nodes and usually but not always of the spleen. The blood count is normal and it is difficult to differentiate the condition from a simple hyperplasia. The enlargement of the lymph nodes is due to enormous enlargement of the lymph follicles which compress the intervening lymph sinuses. The follicles appear like huge germinal centers. Under higher magnification the cells are typical lymphoblasts. The capsules of the gland show a tendency to invasion, which becomes permanent in the later stages. The spleen when enlarged may reach enormous dimensions. Microscopically, it is thickly studded with large Malpighian bodies of similar morphology to those in the lymph nodes. Their enormous number proves that they do not represent hyperplasia but a new formation of giant follicle-like structures. The process may involve tissues that contain but small quantities of lymphoid tissues, for instance, the orbit (leading to proptosis), the breast, the lachrymal glands, the subcutaneous fat, etc. Strangely enough, the tonsil and the lymphoid tissues of the gastrointestinal tract are never affected. Serous and chylous effusions in the pleura and peritoneum are common and are due to compression of the lymph sinuses interfering with the flow of lymph.

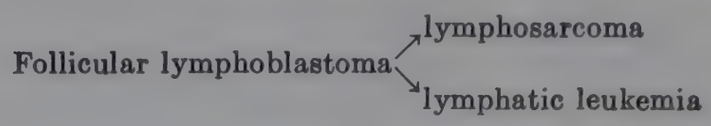
The disease usually presents a milder course than the conventional lymphosarcoma and is particularly radiosensitive so that both glands and spleen may melt away after only a few applications of the Roentgen rays. Unfortunately, the disease does not remain cured; in the majority of cases, the disease returns,

sometimes after many years (4 to 15 years), the glands become Roentgen resistant and the patient succumbs. The morphology of the glands now bears every resemblance to those usually seen in the ordinary type of lymphosarcoma. Symmers (3) and Sugarbaker and Craven (4) reported a number of similar transformations. In 1932, Baehr reported that 8 out of 19 patients died and 8 of those who could be followed were still alive at the end of between one and fourteen years.

Another eventuality of follicular lymphoblastoma is chronic lymphatic leukemia. Baehr and Klemperer (2) saw two cases, Symmers (3) four and Gall, Morrison and Scott (4) one case.

It is very evident therefore that follicular lymphoblastoma is in most instances, the forerunner of lymphosarcoma and less frequently of lymphatic leukemia.

The Biology of Follicular Lymphoblastoma

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CHAPTER 9

# MYELOMA

Although myeloma is no longer as rare as it was formerly deemed, the biology of the disease is nevertheless only dimly understood, because the opportunities to witness the evolution from its very beginnings come but rarely. Moreover like all malignant neoplastic diseases, the malady is dormant long before sufficiently diagnosticable manifestations appear. Myeloma possesses a comparatively long life cycle and although the average duration of life from the onset of clinical manifestations is between two and three years, reports of durations of five to ten years are by no means rare; in one case it was $14\frac{1}{2}$ years (1).

The following presentation is based on a few personal observations and a study of reported cases. We do not propose to review all the manifold clinical signs and symptoms of this fascinating disease, but only those that may have a biological significance.

1. *Pathologic Anatomy.* In most instances, the first symptom is pain, localized to one or other area of the skeletal structure, and usually x-ray examination reveals multiple areas of rarefaction throughout the bony structures. However diffuse myelomatosis may occur without positive x-ray evidence, as shown by biopsy and especially by sternal puncture. There have been frequent reports of solitary myeloma (2, 3, 4, 5) which are supposed to have a better prognosis than the generalized form. Such solitary myeloma may easily be confused with hyperparathyroidism. Most of these solitary myeloma were reported before diagnostic sternal puncture was available, and without an adequate follow-up. Since then the number of reports of "solitary" myeloma has dropped appreciably; first, because sternal puncture reveals generalized involvement (3) and second, because a follow-up showed both clinical and x-ray evidences of general involvement. Such a study necessitates many years of observation. Thus King (2) reports a patient who, five years after removal of a solitary myeloma of the hip, showed involvement of multiple ribs and Bence-Jones protein in the urine. The patient felt well and was still alive at the last report. Vihvelin's patient (6) was alive 12 years and felt well following removal of a solitary myeloma, although clinical evidences of a generalized "recurrence" were clear. It is apparent, therefore, that the reports of solitary myelomata, both as regards

its validity as an entity and its prognosis must be viewed with skepticism. Obviously we have no way of determining whether myeloma begins as a localized disease or multicentrically. In its terminal phases it is always diffuse.

Although the disease is usually limited to the bone marrow, extraosseous growth, especially of the lymphatic structures, has been reported and when these represent the original manifestations of the disease, the diagnosis of plasmacytoma is made. In one case (7) clinical evidence of typical myeloma of the bone with Bence-Jones protein in the urine appeared eight years later. It is questionable whether such "plasmacytoma" represents a separate entity, as some aver, or not. Jackson and his coworkers (7) do not believe so and regard both myeloma and extramedullary plasmacytoma as different manifestations of a generalized neoplastic disorder of the lymphatic system. The matter of classification of plasmacytoma and myeloma is confused by the fact that the plasma cell and the myeloma cell resemble each other so closely, and what appear to be typical instances of myeloma are reported as of the plasma celled type, and reversely. Whether such a distinction is valid is questionable, because both are derived from the same parent cell—the lymphoid type. There are undoubted plasmacytomata that are extraosseous and remain extraosseous. These have been recently reviewed by Hellwig (8). The extramedullary myelomatous invasion of parenchymatous organs, for instance the liver, spleen and kidneys, associated with an unusual invasion of the circulating blood with plasma cells creates another variant that has been termed "plasma cell leukemia" (9). Most of the reported cases of "plasma cell leukemia" are associated with myeloma of the bone, Bence-Jones proteinuria, and hyperproteinemia, and many are accompanied by plasma or myeloid infiltration of the parenchymatous organs. To call such cases plasma cell leukemia is entirely a matter of definition of the term leukemia. Piney and Reach (11) go so far as to divide myeloma into the leukemic and aleukemic types. Rubinstein (10) postulates that myeloma bears the same relation to plasma cell leukemia as lymphosarcoma to lymphatic leukemia. Observers have reported a host of other variants in respect to the topography and distribution of the myelomatous lesions, the invasion of the blood stream by plasma cells and the presence or absence of Bence-Jones protein in the urine, and have attempted thereby to define separate disease entities; but from the strictly morphological and especially biological point of view, these variants represent one and the same disease, namely myeloma.

*Blood changes in multiple myeloma.* Aside from a progressive secondary anemia which may be very severe, the most dramatic change when it occurs, is an invasion of the peripheral blood with young leucocytes, mostly plasma cells and myelocytes. We have already referred to the occasional invasion of such an unusual percentage and number of these cells as to resemble leukemia. In one case (12) there were 60,000 cells of which 65 per cent were plasma cells. In another (11) there were 23,000 cells with 16 per cent plasma cells, and 8 per cent myelocytes. Patek and Castle (9) report a case with 50,000 leucocytes of which 33 per cent were plasma cells. Most of such reports represent counts

made in the terminal phases. When counts are made serially from the early to the terminal phases, there is as a rule a progressive rise both in number and percentage of the young forms. Thus Rubinstein (10) reports a rise in the total white blood cell count from 6,000 to 26,000 and a percentage increase of plasma cells from 0.5 to 38 per cent. However, plasma cells may never appear in the blood at any stage, even when there is a pronounced myeloid invasion of the parenchymatous organs as in the case of Churg and Gordon (13). The cause of the variable invasion of the peripheral blood is not clear.

A hyperproteinemia of 9 mgm. per cent or more is found in most of the reported cases. In one case a level of 17.58 Gm. per cent of plasma protein was determined (14), and levels of 12 Gm. per cent are common. Statistics on the incidence of hyperproteinemia in myeloma are almost valueless: first, because very few early cases have been reported; second, because of the paucity of serial determinations; third, because little consideration has been given to the fact that the protein level may be modified by other factors, notably, protein starvation, cachexia and the loss of globulin in the urine; and fourth, because a case with a normal protein level or a hypoproteinemia is less likely to be reported. An average general incidence may be gauged by reports of groups of cases by one observer. Thus Magnus-Levy (15) in 5 cases noted a hyperproteinemia in 3; Feller and Fowler (16) in 10 cases noted it in 3; but even in these, the incidence would probably be modified by the above considerations. This will be discussed more fully later. In some early reports (17, 18, 19) the hyperproteinemia was ascribed entirely to an increase of Bence-Jones protein in the blood, but the observers' technique is open to criticism, inasmuch as it did not adequately differentiate between Bence-Jones protein and euglobulin; moreover there is, as yet, no available method of estimating the quantity of Bence-Jones protein in the blood except roughly. With more refined methods, especially by fractionization, ultracentrifugation and precipitation methods, it has been fairly well determined that the concentration of Bence-Jones blood protein is only a small portion of the total (20, 21, 22, 15). All observers agree that with rare exceptions, the largest increments in producing the hyperproteinemia of myeloma are the globulins, especially the euglobulin fraction. In exceptional instances, it is the pseudoglobulin i. (23); in addition, minor protein increments may be present, pseudoglobulin ii, fibrinogen (24) and some unclassified proteins (23). The hyperglobulinemia and the occasional high fibrinogen content is responsible for the positive formol-gel reaction and autoagglutination so commonly observed in myeloma. Hyperglobulinemia is not distinctive of myeloma, since it occurs in most instances (aside from hemoconcentration) in which a hyperproteinemia occurs; for instance, in lymphogranuloma venereum, and in kala azar; also in all such conditions, the albumen fraction is decreased; in consequence there is a reversal in the albumen-globulin ratio. The cause for the development of hyperproteinemia in myeloma is not known. It has been suggested (25) that the blood Bence-Jones protein acts as a foreign protein, causing a rise in globulins similar to that occurring after injecting foreign protein (26). This would only be possible provided Bence-Jones protein in the blood was always accompanied

by a hyperproteinemia. Apparently this does not always hold true. In one case (27) apparently large quantities of Bence-Jones protein were present in the blood and for a period of at least 5 months, but the blood proteins remained consistently normal.

There appears to be no relation between hyperproteinemia or hyperglobulinemia, and the presence of Bence-Jones protein in the urine (23, 21, 24).

The hyperglobulinemia may be the explanation, in part at least, for the local and generalized amyloidosis that is sometimes associated with myeloma (28, 24, 29) since there is evidence (30, 31) both clinical and experimental that hyperglobulinemia frequently precedes the deposition of amyloid.

*Bence-Jones protein in urine and blood.* Our incomplete knowledge of the biology of myeloma is reflected in the paucity of data concerning the time relations in the incidence of both Bence-Jones proteinuria and Bence-Jones proteinemia in myeloma.

Although the quantity of Bence-Jones protein in the urine is slightly modified by the protein content of the diet (15) it has been fairly established by precipitation tests and by metabolic methods that Bence-Jones protein is entirely endogenous in origin (32, 33, 34, 35) and represents a substance manufactured by the myelomatous tissue. Fleisher (36) and Meyler (37) found Bence-Jones protein in normal marrow. If this is confirmed, the conception that Bence-Jones protein arises from the neoplastic myelomatous tissue would be considerably fortified. The incidence of Bence-Jones proteinuria in myeloma has been variously estimated; 65 per cent according to Geschichter and Copeland (38) and 73 per cent according to Magnus-Levy (15). These incidences as in the case of hyperproteinemia, are probably specious; first, because the method of determination is faulty. This is particularly evident in cases in which there is a large admixture of serum protein in the urine. Second, because it has been shown by Miller and Sweet (39) that when a urine containing protein is allowed to stand 8 to 24 hours, a reaction simulating that of Bence-Jones protein may be obtained; and third, because the presence or absence of Bence-Jones proteinuria depends to a certain extent on the stage of the disease. In two cases that I have observed, Bence-Jones proteinuria was absent (in one case for nearly a year), although the diagnosis of myeloma was established in both. In both instances Bence-Jones proteinuria developed subsequently. Nevertheless there is little doubt that Bence-Jones proteinuria may be absent throughout the course of the malady, despite the fact that the blood contained considerable amounts of Bence-Jones protein (27). Magnus-Levy (15) found that the longer the duration of the disease the greater the likelihood of its presence. The reason for its absence in some instances is not clear, because the molecular weight of Bence-Jones protein is about 35,000 (40) as compared to that of serum albumen which is 67,500, so that one would expect it to pass through the glomerular capillaries (40). It has been suggested that in such instances, the Bence-Jones protein is in the form of some complex, perhaps in combination with another protein making it of larger size (20). Hopkins and Savory (36) have shown that other factors aside from more permeability condition the passage of Bence-Jones protein from the blood into the

urine. These are, among others, the acid and salt concentration of the media. We have already remarked that Bence-Jones proteinuria is frequently associated with a serum albumen proteinuria. Sometimes only serum albumen is present (41). Exceptionally neither serum albumen or Bence-Jones proteinuria occurs although Bence-Jones proteinemia is demonstrated (23). These relations are poorly understood, but unquestionably time factors must be considered as well. One might assume, in some cases at least, that the constant passage of Bence-Jones protein in the urine may injure the kidney sufficiently as to permit the escape of serum protein into the urine. There is suggestive evidence therefore. In one case under my observation, Bence-Jones protein was the only protein found in the urine in the early phase. Terminally, larger quantities of serum protein were additionally excreted. Further evidence is afforded by the well controlled experiments of Forbus and his collaborators (42). Under normal circumstances, the injection of pure Bence-Jones protein into animals, if the dose is large enough, leads to a rapid excretion of the protein (40). Forbus and his collaborators (42) injected large amounts over a prolonged period and produced a mild form of the characteristic lesion described by Thannhauser and Krauss (43), and Bell (41) in myeloma, namely, a plugging of renal tubules with casts of a peculiar almost crystalline structure, consisting of precipitated globulins. This is the lesion that contributes largely to the renal insufficiency so frequently reported in myeloma. It is interesting to note that these animals persistently voided serum albumen, even when no Bence-Jones protein was passed. The incidence of such a sequence in human myeloma cannot be judged from reported cases, because almost all represent static or almost static observations. One may conceive that if under such circumstances the amount of serum protein is sufficiently large and voided over a protracted period, that a hyperproteinemia might be restored to a normal serum protein content or even to a hypoproteinemia. In a tabulation that I made of reports in which the amount and partition of serum proteins are given together with the approximately quantitative tests for both albumen and Bence-Jones proteinuria, it appears that by and large, the highest levels of serum protein are associated with none or little albumen proteinuria, while the lower levels of serum protein are associated with a more abundant albumen proteinuria.

There is a broad correspondence between proteinuria and the total blood serum protein. The higher the proteinuria the lower the total blood serum protein and vice versa. However, the correspondence is by no means consistent, and there may be other factors in myeloma beside urinary loss that lower the serum protein; for instance, cachexia and protein starvation. The excretion of Bence-Jones protein apparently has little effect on the hyperproteinemia, which is to be expected, considering that it is an endogenous product. The study of the biology of myeloma is nicely illustrated in the report of Chester (44), who upon the first examination found a total serum protein of 7.65 mgm. per cent of which 4.04 per cent was albumen and 3.61 was globulin. One year later the total serum protein was 4.93 mgm. per cent of which 3.21 was albumen and 1.72 globulin. During this entire period of observation, the patient

passed not only Bence-Jones protein but large quantities of serum albumen in the urine. Magnus-Levy (28) points out that when amyloidosis complicates myeloma, large amounts of protein may be additionally lost in the urine.

*Bence-Jones proteinemia and its relation to Bence-Jones proteinuria.* Clinicians were long puzzled by the curious discrepancy between the high incidence of Bence-Jones proteinuria and the low incidence of Bence-Jones proteinemia. Even when Bence-Jones protein was reported to be present in the blood, the validity of the finding has been questioned because the characteristic precipitation between 45° and 60°C. and its complete solubility at 100°C. did not sufficiently differentiate Bence-Jones protein from euglobulin (20). More modern methods obtained by fractionization, by extraction, solubility curves, ultracentrifugation, and specific precipitation tests (since Bence-Jones protein acts as an antigen) (45, 46) have amply demonstrated its presence not only in the blood but in pleural fluid (47) and the pericardial exudate, but not in the cerebrospinal fluid (48). Further, by the technique of electrophoresis most sera from patients with myeloma reveal characteristic patterns (20, 23), that appear in no other malady; these patterns in part represent Bence-Jones protein, as proven by the observation that Bence-Jones protein isolated from the urine when added to normal serum gives the specific pattern (20, 23). In fact, by the electrophoretic method, a protein, presumably Bence-Jones protein, was detected in the serum, when the fractionization method of Howe did not reveal it. Moore and his coworkers (20) in their 7 cases of myeloma found a correlation between Bence-Jones proteinemia, even when there is no excretion of Bence-Jones protein in the urine, "the possibility of significant Bence-Jones proteinemia is not excluded, because interaction in the serum may result in the formation of nonfilterable substances." In the light of these newer data, the entire problem concerning the incidence of Bence-Jones proteinemia and its relation to Bence-Jones proteinuria will necessitate complete revision. The problem is further complicated by the fact that Bence-Jones protein is not a single substance (45, 49) but two or three substances as determined by precipitation tests; that electrophoresis in myelomatous sera reveals hitherto unclassified proteins (23), and that thus far we have only approximate methods of determining the quantity of these substances.

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CHAPTER 10

# GRAVES' DISEASE

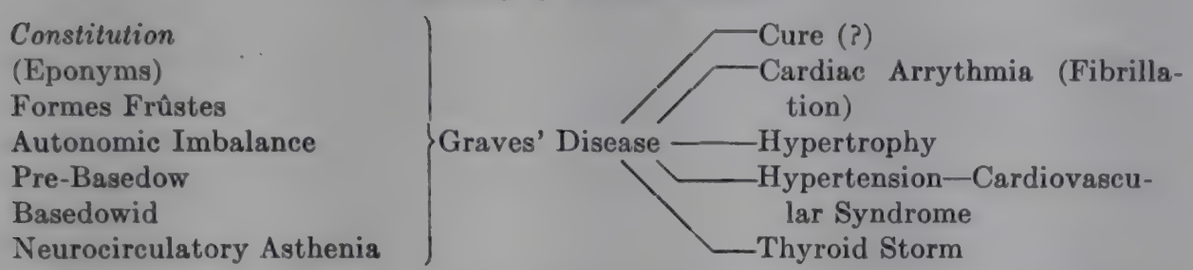
The diagnosis of Graves' disease is obvious when the classical quadrad of signs, namely tremor, tachycardia, swelling of the thyroid gland and exophthalmos, are present. Difficulty enters into the strict nosological status of the exceedingly common group of patients who present the characteristic neuropathy but in whom one or more of this quadrad of signs are absent. For instance, exophthalmos is missing in about one quarter of the cases (23.2 per cent-Sattler) (1) and in about the same proportion there may be no swelling of the thyroid gland. Even a tachycardia of appreciable degree may be absent, and a tremor is by no means constant. While such patients are usually sensitive, emotional, overstimulated, anxious, irritable and reveal great swings between ecstasy and depression, even this neuropathic personality may not be prominent, constituting the rare cases of the so-called "apathetic" types of Graves' disease. In my experience however, the apathy is more apparent than real, and on deeper analysis the apathy is found to be a mask rather than a state of mind.

These abortive cases have received different names in the past; *formes frûstes*, autonomic imbalance (2), Basedowid (3), pre-Basedow (4), and neurocirculatory asthenia. Between this primitive type and the complete end product comprising the quadrad of cardinal signs, one finds an endless variety of clinical combinations: tachycardia, tremor and enlarged thyroid gland without exophthalmos; tachycardia, tremor and exophthalmus without an enlarged thyroid; tremor and tachycardia without exophthalmos or an enlarged thyroid gland, etc. Most observors have been unwilling to classify these larval forms within the domain of Graves' disease, unless the basal metabolic rate is elevated. Such a conclusion is based upon a static rather than the dynamic or biological viewpoint of disease processes and has created a number of fallacies.

1. It is fallacious to believe that the symptom complex at the time when it was observed had attained its fullest fruition, and was not merely a phase of a process whose natural history extended long before and projected long after the period of observation. I have had the fortunate experience of witnessing the development of classic Graves' disease in a number of patients whom I have watched closely for many years previously. These were sensitive, sanguine, quick, overstimulated, introvert, emotionally unstable folk and possessed a temperament that I

have called "allergic to life." They reveal a strong manic depressive life curve. They often give a history of "nervous diarrhea." These attributes are usually traceable back into childhood. The eyes were bright and under emotional stimuli, the pulse became rapid, tremor developed, they flushed easily and the eyes became starey. If the emotional insult continues, these manifestations lost much of their lability and became more or less fixed. The basal metabolic rate at this time while within the range of normal, veers to the plus side. If the emotional insult is profound or protracted, one witnesses the process of hyperkinesis (5) with an exaggeration and greater fixation of these signs. The tremor and tachycardia persist, the eyes become exophthalmic, the thyroid may begin to swell and the basal metabolic rate attains abnormal levels. Soon weight loss and excessive sweating ensue, and the clinical picture of Graves' disease is then complete.

*Biology of Graves' Disease*




The type personality I have described plus the individuals reaction to the environment represents the constitutional factor in Graves' disease that has been emphasized repeatedly (6–9) and differs in no way from that implied in the terms *formes frûstes*, autonomic imbalance, Basedowid, pre-Basedow, and certain instances of neurocirculatory asthenia.[1]

Opinions are various as to whether this constitution is congential or acquired, but Lorand and Moschcowitz (10) have submitted strong evidence that it is largely conditioned by environmental factors, in which parental overprotection plays by far the dominant role. There is little ground for assuming that anatomical characters form part of the constitution. There is no particular physical conformation that is prone to acquire Graves' disease. The very frequent association of status thymico-lymphaticus and Graves' disease, has afforded to some, especially Warthin (11), grounds for holding that anatomical characters partake in this constitution. I have discussed this relationship (12) and have submitted evidence that indicates that the status thymico-lymphaticus represents one of the backgrounds that notoriously renders the patient extraordinarily sensitive to both physical and emotional stimuli.

2. It is fallacious to believe that the measurement of the basal metabolic rate constitutes a decisive differential between Graves' disease and the abortive forms represented under the terms autonomic imbalance, etc. Inasmuch as the basal

[1] Bernstein and I have adduced strong evidence that most cases of neurocirculatory asthenia are the larval phase of Graves' disease. Among other evidence, we cite 12 cases observed in The Mount Sinai Hospital, in which on the first admission the diagnosis of neurocirculatory asthenia was made and on a subsequent admission, Graves' disease.

metabolic rate measures in part at least, the degree of thyroid activity, the term "hyperthyroidism" is conventionally regarded as synonymous with Graves' disease. I believe this is entirely arbitrary and unwarranted and has tended to perpetuate other current subsidiary fallacies regarding the nosology of Graves' disease. My reasons for this viewpoint are the following:

a. Administration of active thyroid preparations even over a prolonged period mimics but never completely reproduces the clinical picture of Graves' disease (13);

b. After thyroidectomy the basal metabolic rate usually drops to normal but many of the cardinal evidences of Graves' disease may persist, often permanently. The one factor that always remains is the underlying personality or constitution, which is always potential to flare up into the active stage of the disease, given the proper environment. Under such circumstances, the diagnosis assuredly does not change because the basal metabolic rate has returned to normal.

c. Most clinicians are familiar with so-called "spent" cases of Graves' disease, i.e. patients who reveal all the clinical evidences of the disease, although the basal metabolic rate is within the normal range. This, of course, does not imply that at some previous stage, the basal metabolic rate had not been elevated; it probably was, but in diagnosis one can only be concerned with data obtained at the time of observation.

On a priori grounds, it is unreasonable to expect that the basal metabolic rate can be a decisive differential, because the range between which the rate +15 to −15) is regarded as within the normal is entirely arbitrary. For purposes of diagnosis, the determination of the basal metabolic rate has precisely the same value as thermometry in febrile disorders. It is entirely a measurement of activity and more particularly of the hyperthyroid component in the totality of the clinical expression. Graves' disease may therefore be represented in the following equation:

Constitution + hyperthyroidism = Graves' disease. Being therefore a hyperkinetic disease, the diagnosis of Graves' disease cannot depend upon a specific test such as for example the finding of tubercle bacillus in suspected tuberculosis, but on a study or reconstruction of the total organ-personality. The history in a patient with Graves' disease, therefore, does not begin with the onset of the signs and symptoms, but at birth, and should comprise the story of all the parental, familial, social, economic and sexual influences; his loves, his hates, and the fears to which the patient has been subject.

There are many who hold that the diagnosis of Graves' disease can only be established by finding the characteristic hyperplasia of the thyroid gland. This can hardly be valid, because such a hyperplasia is absent in about 10 to 15 per cent of the cases (14–16).

The biology of Graves' disease, however, does not culminate when the transition from the larval or constitutional phase to the fully developed form has been attained. Henceforth its possible evolutions, if the progress of the malady is not checked, are various.

1. As a result of the persistent tachycardia and the consequent increase in

volume output, the heart hypertrophies. In time left ventricular failure ensues and eventually failure of the right heart with hypertension of the pulmonary circuit (see Chapter 1).

2. An arrhythmia develops, nearly always auricular fibrillation, again with the sequence of left and right ventricular failure.

3. Hypertension ensues. This eventuality is especially common in patients within the older group, but it is by no means uncommon in younger patients, masking in the form of "diencephalic" hypertension (17). In a number of instances, I have had the opportunity of witnessing the development of hypertension in patients with "spent" Graves' disease. As a result of the high pulse pressure characteristic of Graves' disease with a comparatively low diastolic pressure, there is at first a compensating rise in systolic pressure. In time the diastolic pressure also rises, and as the process continues, both systolic and diastolic pressures rise to real hypertension levels. Eventually, usually after many years, the cardiovascular syndrome develops precisely similar to that described in hypertension of the greater circulation (see Chapter 2.)

4. Thyroid storm. This may occur either spontaneously or after operation. Fortunately, with the introduction of Lugolization this tragic eventuality occurs less frequently than before.

5. Certain mild cases pursue what apparently appears a favorable course upon, what some writers term, "skillful neglect." The pulse slows, the tremor subsides, the basal metabolic rate returns to normal levels, and the patient returns to a social and economic adjustment. But the psyche or in other words, their constitution remains, which henceforth usually reacts like a hairtrigger to the buffetings of their environment; they remain unstable, anxious, develop tremor and tachycardia under the slightest provocation, and in an appreciable number of instances, if the provocation is intense and prolonged, develop a genuine Graves' disease. It is reasonable to infer that temporarily these patients have lost the hyperthyroid component.[2]

The identical sequence of events occurs after subtotal thyroidectomy. The operation, so to speak, amputates the hyperthyroid component. The reduction of the basal metabolic rate accomplishes much by reducing or even eliminating many of the hyperkinetic phenomena. The tremor and tachycardia subside, the excessive sweating and agitation is reduced, the weight begins to rise, a peaceful sleep is restored. But the underlying psyche or constitution remains, again potential, given the proper environment, to bring forth a recurrence. A patient with Graves' disease is never completely cured in the sense that one cannot predict with any assurance that a recurrence will never take place. For this reason, as we have previously insisted, the treatment of the patient with Graves' disease only begins when the operation has been finished.

Often enough, and especially if the disease is protracted, the operation may

[2] It is well to be reminded that of the total metabolism the thyroid gland contributes only 40 per cent (18). To what extent the basal metabolic rate in Graves' disease represents thyroid activity alone or is derived from the total metabolism can only be determined by total thyroidectomy, an operation which is not generally done in this disease.

only reduce the hyperkinetic phenomena to a lower order of activity; tremor and tachycardia are lessened, the basal metabolic rate hovers around the upper limit of the normal or even slightly higher, sweating continues and the weight remains stationary. They remain "nervous" anxious and fearful. In other words, the cycle reverts itself. A number have been reported (19, 20, 21) as having developed the complication (?) "neurocirculatory asthenia." If a true recurrence of Graves' disease does not occur, some develop the cardiac or cardiovascular sequelae outlined in 1, 2 and 3. This statement is based not only from direct observation for a sufficiently long period in a few instances, but also by reconstruction of the life history in certain patients with cardiac disease, the origin of which seemed obscure.

To summarize, Graves' disease is a psychosomatic disease and its clinical expression represents a hyperkinesis of many normal bodily functions, the dominant one being the normal basal metabolic rate. The background is a constitution mostly psychic in makeup largely conditioned by environmental factors, and the disease attains its fullest fruition usually as a result of either a catastrophic or a prolonged psychic strain. Between the background and the fully developed form occur a host of clinical expressions that have received different eponyms in the past. These merge into themselves so imperceptibly that it is sometimes extemely difficult to determine when the disease begins and when the constitution ends, and it is only by a study or a reconstruction of the total organ-personality together with an adequately prolonged follow-up that the biology of the disease can be recognized. By so doing, the biological course will be found to be in both directions, sometimes forward toward hyperkinesis and sometimes the reverse, toward regression, depending upon the individual's reaction to his environment.

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CHAPTER 11

# THE RELATION OF NEUROCIRCULATORY ASTHENIA TO GRAVES' DISEASE*

## INTRODUCTION

This rather ill-defined disorder, without a background in morbid anatomy, which has at various times been called "effort syndrome," "disordered heart action of soldiers," "autonomic imbalance," and (from its discoverer) "Da Costa's syndrome," has not obtained the dignity of a nosological entity. Because of the vagueness of its clinical outlines, both symptomatic and objective, its definition is more or less arbitrary, and, for this reason, the term syndrome seems decidedly more applicable. We believe the failure to place this syndrome into its proper category is due to the current tendency to view disease from the static rather than the dynamic viewpoint, and the failure to grasp the fact that biology (1) has its role in the interpretation of disease processes. If this view is taken, neurocirculatory asthenia presents so many features in common with the larval, or constitutional, phase of Graves' syndrome that we believe the two are identical, and it is with the exposition of this thesis that this paper is concerned. Indeed, the resemblance between the two maladies is so strong that most writers who believe in the specificity of neurocirculatory asthenia as a disease entity concern themselves with the differential diagnosis of this malady from Graves' syndrome. This concept is not new; it has been broached a number of times, especially during the last war by Barr (2), Brooks (3), Carrol (4), and Grotti (5), but on what we believe to be insufficient evidence.

In order to elucidate our thesis, we shall take up the various clinical characteristics of neurocirculatory asthenia, as currently described, and show their similarity to those of Graves' syndrome.

*Symptomatology.*—The conventionally described symptoms of neurocirculatory asthenia are breathlessness (especially on effort), palpitation, fatigue, dizziness, occasional precordial pain, sighing respiration, headache, dry mouth, occasional syncope, and diarrhea. Usually, there is anorexia. Sir Thomas Lewis (6) describes this attitude as "frozen with fear with wide staring eyes." Moreover,

* Written in collaboration with Solon S. Bernstein, M.D.

these symptoms are not by any means strictly related to war, but occur even in adolescents, especially under the influence of emotion (7–11). This fact, coupled with others that we shall mention, effectively disposes of the notion that neurocirculatory asthenia is strictly a war disease. The similarity of these symptoms with those of Graves' syndrome is too obvious to require discussion. In fact, they are identical with those we have often observed in patients under emotional strain, whom we have known well before the onset of the typical Graves' syndrome, and to whom the diagnosis of cardiac neurosis, psychoneurosis, or autonomic imbalance (12) was applicable. Moreover, these symptoms are observed not infrequently for varying periods after subtotal thyroidectomy for genuine Graves' syndrome, sometimes for the remainder of the patients' lives.

*Physical Signs.*—The characteristic physical signs of neurocirculatory asthenia (6) are tachycardia, coldness and blueness of the hands, hyperpnea or tachypnea, tremor, sweating of the palms and axillae, asthenia, and dermographia.

a. Tachycardia: This appears to be the most conspicuous and consistent sign of neurocirculatory asthenia. In the first World War, most observers, and especially Sir Thomas Lewis (6), ascribed the tachycardia to effort, but, in World War II, it is the opinion of most British observers that the tachycardia was due not so much to effort as to emotion. Thus, Jones and Lewis (9) say that "it is not effort but the situation in which effort is required and the emotional attitude of the man toward this situation that are significant factors." They noted, for instance, that, in the carpenter shop, the patients showed no evidence of tachycardia as compared to other forms of training. Wood (7) expresses himself in a similar vein. This effect is comparable to that which one sees in the initial phase of Graves' syndrome. The point is frequently raised that the tachycardia of Graves' syndrome differs from that of neurocirculatory asthenia in that it does not tend to disappear at rest. If we compare neurocirculatory asthenia to the florid and full-fledged type of Graves' syndrome, this is more or less true, but, in the larval, or initial, phase of Graves' syndrome, we have observed repeatedly that, under conditions of emotional and physical rest, the tachycardia subsides.

b. Coldness and blueness of the hands: These signs are by no means always present in neurocirculatory asthenia; according to Wood, this sign was noted in 44.5 per cent, and its pathognomonic significance has been further minimized by the observation of Sir William Osler (quoted by Wood) that, in England, cold, blue hands are exceedingly common because of climatic conditions. Nevertheless, this sign is repeatedly used to differentiate between neurocirculatory asthenia and Graves' syndrome. That the hands are warm in Graves' syndrome because of peripheral vasodilatation (13) is well known, but this is true only in the florid types. In the larval or constitutional phase, before the basal metabolic rate has become elevated, we have noted cold hands as often as not. At best, this sign is indecisive.

c. Hyperpnea and tachypnea: These symptoms are common in emotional

states with or without organic heart disease, and have little significance as diagnostic differentials.

d. Tremor: The tremor is generally believed to be coarser in neurocirculatory asthenia than in Graves' syndrome, but it is questionable whether this is sufficiently decisive to be used as a diagnostic point. In our experience, the tremor varies widely in Graves' syndrome, depending partly on the stage of the disease and partly on the emotional state of the patient. In the constitutional stage of Graves' syndrome, the tremor is more often coarse than fine, and, if absent, it can be induced or intensified by an injection of adrenalin, thus supporting the view of Cannon (14) that, under the stimulus of fear, hyperadrenalemia is induced (Goetsch test). Suggestive in this connection is the observation of Peabody, Clough, Sturgis, Wearn, and Tompkins (15) that the Goetsch test was positive in 60 per cent of their soldiers with irritability of the heart; usually there was a temporary rise in the basal metabolic rate in these cases. Boas (16) found the Goetsch test positive in 29 per cent of his cases. The cause of this difference is not clear.

e. Sweating of palms and axillae: This symptom does not differ in the slightest from that usually observed in Graves' syndrome.

f. Asthenia: It differs in no essential from that of Graves' syndrome.

g. Dermographia: This is exceedingly common in both conditions.

The close similarity between these symptoms and signs and the classical description of Darwin (17) of the expression of fear, which, as we shall see, is the dominant exciting agent of both disorders, is indeed striking. Both Crile (18) and Wood (7) stress this analogy.

*Occurence in Civilian Life.*—That the occurrence of neurocirculatory asthenia is not strictly limited to wartime is obvious to every general practitioner, and, moreover, it is extremely common in civil life. Thus, White and Jones (19) noted it in 302 of 3,000 patients who had cardiac complaints; in 62 additional cases it was accompanied by organic heart disease. The reason for its prominence during wartime is undoubtedly fear. One of us (20) has already called attention to the fact that Graves' syndrome, like most psychosomatic diseases, bears a distinct relation to great crises and emotional waves, and, broadly, to the increased strain of living.

*Age.*—Both neurocirculatory asthenia and Graves' syndrome occur at all ages. The reason for the greater preponderance of neurocirculatory asthenia in the third and fourth decades is the circumstance that this is the military age. Both are rare in children (21) before the emotive and sensitizing faculties are fully developed.

*Sex.*—There is a current notion that neurocirculatory asthenia is a masculine disease because most reports are concerned with soldiers, but it is exceedingly common in women. Indeed, Craig and White (22) and Wood (7) agree that two-thirds of the cases occur in women. As Wood expresses it, "the change of sex and the lack of khaki uniform act as an effective disguise." The preponderance of Graves' syndrome in women is accepted by all.

*Constitutional factor.*—Neurocirculatory asthenia does not affect perfectly normal persons, nor does it arise de novo in such. Most observers (4, 6–10, 23) speak of a constitutional factor. This is evident in the extraordinary frequency of familial incidence. Oppenheimer and Rothschild (10) found "nervousness, insanity, or epilespy in the family in 45 per cent." Wood found a high incidence of psychoneurosis or cardiac neurosis as compared to controls. Parkinson (8) found a family history of symptoms similar to those of neurocirculatory asthenia in 60 per cent of his cases. This does not necessarily imply that there is a genetic factor; far morely likely, the transmission to the son is the result of environmental background and sensitizing factors. Thus, Jones and Lewis (9) found that a large majority of the victims were "spoiled" children, and that the horror of war was often inculcated by the parents. Wood found that, in childhood, most of the patients were delicate, and clung too long to their mothers' skirts. They were filled with apprehension about going to school, and, altogether, the case histories suggested that parental influence induced timidity.

The previous history offers further evidence of the constitutional factor in neurocirculatory asthenia. Most observers agree that the majority present a history of either neurocirculatory asthenia or psychoneurosis before enlisting, often dating back to adolescence. Thus, Oppenheimer and Rothschild found, in 75 per cent of their cases, a history of either stigmata, previous nervousness, fear, moodiness, a previous breakdown, enuresis, frights in childhood, or any of a number of other factors. Boas (23) found that the vast majority gave a history of nervousness and excitability dating back to childhood, and that they could not stand the strain of excitement. They bore a strong resemblance to the cases described by Bass and Wessler (24) in children, many of whom had orthostatic albuminuria. Wood (7) expresses himself similarly, and finds that tics, bed-wetting, nightmares, and stammering are common traits, and that a psychiatric diagnosis, such as a depression, an anxiety state, hypochondriasis, hysteria, etc., could always be made. Jones and Lewis (9) obtained a history of stammering, bed-wetting, and sleepwalking in about 50 per cent, and nearly two-thirds were shy, tense, hypochondriacal, or delinquent. Parkinson (8) found that 50 per cent gave a history of symptoms similar to neurocirculatory asthenia before the war, but not sufficient to prevent them from pursuing their sedentary occupations. Observers are unanimous in their opinion that these patients are exceedingly sensitive to both physical and psychic influences, and are introvert and fearful. There are no anthropologic characters that are peculiar to patients with neurocirculatory asthenia, but most observers agree that they are not athletic in build, action, or spirit.

Taken by and large, there is sufficient evidence of a constitutional factor, and the probability is strong that it is phenotypic rather than genotypic.

These constitutional factors of neurocirculatory asthenia parallel those of Graves' syndrome closely. In a previous communication (20), one of us pointed out the illuminating significance of a family history in Graves' syndrome. The same malady affects two or more members of the family, which is more than the law of averages allows (26–28). What is expecially striking is that few of the

siblings are phlegmatic or adjusted folk; psychoneuroses of all sorts, cardiac neuroses, and even psychoses (29) are frequent, and the symptoms and signs are identical with those of neurocirculatory asthenia.

One of us also called attention to the fact that Graves' syndrome almost always affects persons of a characteristic psychic makeup. They are unusually sensitive and emotional. They respond to their environment, whether physical or psychic, like an aeolian harp, and, in consequence, feel that their lives have been unusually hard. Their emotional range is wide, varying from ecstasy to depression, and, indeed, psychoses of this nature are by no means uncommon (30–32). Occasionally, one sees what appears to be a phlegmatic person with Graves' syndrome (33), but, when one digs deeper, one finds that it is only a mask. This personality long antedates the onset of the disease, even back to childhood, and, moreover, persists after the grosser manifestations of Graves' syndrome have subsided.

These two factors, the familial and the personality, comprise the constitution of Graves' syndrome, and from the study of numerous patients from a psychoanalytic viewpoint (34), we came to the conclusion that the influences that engender this constitution are environmental or the result of parental overprotection, rather than genotypic. That a genetic factor plays a role in the development of Graves' syndrome is indicated by the frequency with which the the thymicolymphatic constitution is present. In the Mt. Sinai Hospital, it was found in over 90 per cent of our cases in which there was a fatal outcome. Warthin (35), in particular, emphasized this factor. Whether this lymphatic constitution exists in neurocirculatory asthenia, we have no means of telling. The relation of this constitution to Graves' syndrome is not clear. Inasmuch as it is well known that persons with the lymphatic constitution are unusually sensitive to both psychic and physical stimuli, this may act as a sensitizing agent.

*Exciting cause.*—Most observers of neurocirculatory asthenia in the army, especially in World War I, emphasize fear as the dominating factor in producing the disease (6–11, 36). The fear is of two kinds: 1) sudden, from some harrowing war experience such as gassing, shell explosion, etc., or 2) anticipated; Wood and Parkinson found that the fear of killing or of being killed was present in the majority of their cases. Highly significant in this connection is the statement of Cohn (36), who, in his inspection of the base hospitals in the week after the armistice (1918), found only rare instances of neurocirculatory asthenia; previously they had been common. Parkinson (8) found that neurocirculatory asthenia was rare in the Navy and Air Forces, for the reason that there is a greater proportion of volunteers in these services. In neurocirculatory asthenia of civil life, Craig and White (22), in a study of 100 cases, found that psychogenic factors such as anxiety, sexual irregularities, an unhappy marriage, pregnancy, menopause, infections, and operations were frequent precipitating causes. In the first World War, some observers believed that neurocirculatory asthenia occasionally followed an infection (6, 10). In World War II, comment was singularly wanting on this score. Thus, Wood (7), with his large experience, feels that the factor of infection is highly unimpressive, and that, when such a

history exists, it is the fear engendered by the infection rather than the infection itself that is responsible.

These observations on neurocirculatory asthenia again parallel those in Graves' syndrome. That emotional crises may precipitate an attack of Graves' syndrome is well known. Indeed, we have observed the malady attain its full fruition within a few days after such a crisis. Among the precipitating events, we recall a robbery, a fire, the death of a close relative (usually a mother), a difficult confinement, a frightful sexual experience, a sudden economic loss, and an unwanted pregnancy. There was a sudden crop of Graves' syndrome in Vienna after the theater horror in the eighties, and after the San Francisco earthquake. We at the Mt. Sinai Hospital were particularly struck with the frequency of Graves' syndrome among German refugees, so that the expression "Hitler Graves' " came into vogue. The essential ingredients in these emotional crises are surprise and fear.

Frequently, one does not obtain any history of a surprise shock in Graves' syndrome. In these cases one usually finds reiteration of smaller and petty insults, or a new situation to which the patient cannot adjust himself, such as an unhappy marriage, a sexual abnormality, unrequited love, economic strain, etc. In these instances, it is often difficult to decide when the transition from the constitutional to the florid phase of the disease occurred. In Graves' syndrome, as well, infection has often been accused of precipitating an attack, but, in our experience (20), as in Wood's in neurocirculatory asthenia, it is not the infection, but the fear induced (even when the infection is trivial) that is the significant factor.

*Basal Metabolism.*—Thus far, we have paralleled neurocirculatory asthenia to Graves' syndrome. It is now necessary to reverse the process because Graves' syndrome contains certain clinical elements which are usually absent in neurocirculatory asthenia, namely, an elevated basal metabolic rate, thyroid enlargement, exophthalmos, and response to iodine. Inasmuch as the development of these features bears a relation to the evolution of Graves' syndrome, a discussion of the biology of this disease is in order.. In a previous paper (20), one of us tried to show that Graves' syndrome does not represent a nosological entity in the sense that it has a well-defined group of signs and symptoms and a consistent background in morbid anatomy, but rather a series of diseases arranged in biologic sequence that have previously received different names. The larval phase is the constitutional stage, which has been called Basedowoid, autonomic imbalance, pre-Basedow or pre-Graves', cardiac neurosis, neurasthenia, etc. The signs and symptoms resemble those of neurocirculatory asthenia so closely that they have often been confused. In the middle phase of the disease, at which time thyroid enlargement and perhaps lid-lag have been added to the other signs, the malady has been called a forme fruste. The final or florid phase consists of the classical quadrad of signs, plus an elevated basal metabolic rate, and is conventionally termed Graves' "disease." Between the initial and final phases one finds various groupings of signs and symptoms; one or more of the quadrad of signs, such as thyroid enlargement and exophthalmos, may even be missing.

Graves' syndrome may be described as a hyperkinetic disease in which many of the physiologic functions are exaggerated. Because of this evolution and the inconsistency of the signs and symptoms, the term syndrome seems preferable. The common denominator in all these groups is the type personality described above, and the proof of this natural history, or life cycle, is not only the fact that, when the opportunity arises (and only the general practitioner has it), one can observe such transitions, but also, and more frequently, regressions to the larval phase under the influence of either spontaneous remission or treatment. The difference between the initial and florid phases of Graves' syndrome is like that between the tadpole and the frog. It is still the same animal, but of different shape and habits.

In most quarters, elevation of the basal metabolic rate is regarded as the vital diagnostic difference between Graves' syndrome and all other conditions that simulate it, and for this reason the terms Graves' syndrome and hyperthyroidism have been used interchangeably. We believe this is entirely arbitrary, and has perpetuated a fallacy that has contributed much to the existing confusion concerning the nature of Graves' syndrome. Because the basal metabolic rate is *usually* elevated in Graves' syndrome, one is not warranted in concluding that the patient does not have Graves' syndrome because the basal metabolic rate is *not* elevated. This error in reasoning is regrettably common in clinical medicine. The basal metabolic rate in thyroid disease measures only the degree of the hyperthyroidism, but Graves' syndrome comprises elements that are not entirely explained by the elevation of the basal metabolic rate alone, and for the following reasons: 1) Patients with "spent" or "burnt-out" Graves' syndrome, who reveal the classical quadrad of signs, may possess a basal metabolic rate within the normal range. This does not imply that at some previous date the basal metabolic rate was not high; it probably was, but, clinically, such patients cannot correctly be said to have hyperthyroidism. Kessel and Hyman (12) classify such patients as cases of "autonomic imbalance," but we believe it would be more logical to call the condition "Graves' syndrome without hyperthyroidism." 2) After subtotal thyroidectomy, when the basal metabolic rate becomes normal, many of the clinical manifestations may persist for years, even though the patient is economically and socially restored. 3) During the larval or middle phases of Graves' syndrome, the basal metabolic rate is usually normal, but when, under an emotional strain, the disease assumes a florid form, with a rise in basal metabolic rate, are we justified in assuming that a different disease has been born? All we may say is that the patient has acquired hyperthyroidism. 4) The administration of toxic doses of thyroid extract to human beings mimics, but by no means completes, the clinical picture of Graves' syndrome. One obtains tachycardia and tremor and even weight loss, but no exophthalmos or swelling of the thyroid gland. In animals, Carlson (37) found that excessive doses of thyroid caused only loss of weight, gastroenteritis, and diarrhea. 5) Cases in which there are clinical evidences of Graves' syndrome associated with myxedema occur, even if but rarely. They usually represent

exhaustion phenomena (38–40). Sattler (27) cites a number of instances in which Graves' syndrome was engrafted on myxedema. Hyperthyroidism, as measured by the basal metabolic rate, may be regarded as the most important sign of Graves' syndrome, and it is to the reduction of this rate to normal levels that therapeutic efforts are largely devoted. It is a sign of activity comparable to fever in infections; when the temperature of a patient with typhoid fever returns to normal, he has not necessarily lost his disease. There is abundant evidence (5, 26, 35, 41, 42) that Graves' syndrome is by no means a disease exclusively of thyroid origin. The hyperactivity of the thyroid gland is only a link in the complicated mechanism whereby the disease arises, probably by way of the vegetative nervous system, with involvement of some of the other endocrine glands as complicating factors. The diagnosis of Graves' syndrome should not be dependent upon one or even a group of signs or symptoms, but upon a study of the total organ-personality. Evidence is accumulating rapidly that it is a psychosomatic disease (43–48) and a disease of the higher civilizations. Most observers agree that it is absent in primitive races (41, 49). Particularly illustrative in this connection is the observation that, whereas formerly Graves' syndrome was extremely rare in Negroes, it is at present by no means uncommon, at least in our experience, among northern Negroes. We believe this increase is the result of industrialization and the production of increased conflict that they have acquired in their contact with whites.

If these points of view are accepted, it renders many of the curious, reported inconsistencies concerning the relation of neurocirculatory asthenia to Graves' syndrome understandable. For instance, numerous writers (50–53) report the association of neurocirculatory asthenia with Graves' syndrome because symptoms of neurocirculatory asthenia remain after thyroidectomy. In our experience, this is more common than is usually estimated. Our interpretation is that thyroidectomy does not cause a divorce between two separate diseases, but only between the hyperthyroidism and the neurocirculatory asthenia. In other words, throidectomy simply modifies the clinical picture by causing a regression to the larval stage. On the other hand, reports of an elevated basal metabolic rate in neurocirculatory asthenia are by no means infrequent. The incidence would probably be much more common were it not that most observers begin with a prejudice based on preconceived criteria of both diseases. As soon as the basal metabolic rate is found to be elevated the possibility of neurocirculatory asthenia is promptly excluded. Peabody, Wearn, and Tompkins (54) report the results of measuring the basal metabolic rates of 59 patients with "irritable heart of soldiers." It was within 10 per cent of normal in 48 cases, and within 15 per cent in 53. In two cases, it was 60 and 61 per cent above normal. These were regarded as cases of Graves' syndrome. In three cases the basal metabolic rate was 16 to 22 per cent above normal. These latter cases were not regarded as Graves' syndrome.

A number of observers are puzzled by "borderline" cases between neurocirculatory asthenia and Graves' syndrome, i.e., patients who present most of the

clinical evidences of Graves' syndrome, including tachycardia, tremor, exophthalmos, and goiter, but have a normal basal metabolic rate (35, 50–52). We believe this quandary would vanish if the distinction between hyperthyroidism and Graves' syndrome were recognized.

*Thyroid Enlargement.*—That thyroid enlargement is not essential in the diagnosis of Graves' syndrome is attested by the frequency with which it is absent. It is difficult to estimate the exact incidence because this sign is subject to individual interpretation; according to different observers it varies between 25 and 50 per cent. Data in regard to thyroid enlargement in neurocirculatory asthenia vary widely. Thus, Sir Thomas Barr (2) found it in all cases of "soldier's heart"; Kessel and Hyman (12) found it in 72 of their 86 cases of "autonomic imbalance;" Brooks (3), who leaned strongly toward the view that neurocirculatory asthenia and Graves' syndrome are identical, found a prominence of the thyroid gland in two-thirds of his cases. Boas (23) and Lewis (6) found that 4 per cent of the patients in their series had palpable thyroid glands. McCullagh (56) stated that thyroid enlargement occurs often; Crile (18) took a similar view. Kerr and Addis (57) found that the incidence of thyroid enlargement in recruits with neurocirculatory asthenia was no higher than in a series of controls. Craig and White (22) found only 2 per cent with goiters. This wide variability among different observers affords opportunity for a number of reflections: 1) The confusion in the standards of diagnosis; 2) that the two maladies overlap; 3) that different phases of Graves' syndrome were being observed. Under any circumstance, the absence of thyroid enlargement in the early or neurocirculatory phase of Graves' syndrome does not exclude the diagnosis of Graves' syndrome, because one sees, all too often, the development of goiter in such patients. In other words, it is a later sign of Graves' syndrome. It would be equally valid to claim that, when albuminuria arises in the course of essential hypertension, a new disease has been engrafted. The probability is very strong, therefore, that Kerr and Addis (57) observed their cases in the larval phase (recruits), and that Kessel and Hyman (12) saw theirs in the later stages (hospital) of the malady.

*Exophthalmos.*—As with goiter, exophthalmos is also a symptom of the later, often the terminal, phase of Graves' syndrome. In genuinely florid cases, it is occasionally not present at all—according to Rienhoff (39), in about 50 per cent. Nevertheless, it is interesting to note that what may be regarded as initial evidences of this sign are frequently seen in neurocirculatory asthenia. Thus, Sir Thomas Lewis (6) describes, as characteristic, the look of "frozen fear with wide eyes," and Barr (2), the larger visible area of the sclera. Lewis also admits that "a few developed ocular signs." In the constitutional phase of Graves' syndrome, one of us has described widening of the palpebral fissure and lid-lag as common accompaniments, especially under excitement or even on moderate emotion. Kessel and Hyman (12), in their series of eighty-six cases of "autonomic imbalance," found a von Graefe sign in nineteen and exophthalmos in twelve. Brooks (3) found that exophthalmos was common. Apparently, the status of exophthalmos as a differential criterion between neurocirculatory

asthenia and Graves' syndrome depends, like the basal metabolic rate and thyroid enlargement, upon the phase of the disease in which the patient is observed.

*Response to Iodine.*—Most observers agree that iodine is of no avail in neurocirculatory asthenia, and, similarly, that it is useless in Graves' syndrome without hyperthyroidism. For this reason, the type of response to iodine in the two conditions, as some claim (58, 59), cannot be deemed a diagnostic criterion.

*Transition of Neurocirculatory Asthenia to Graves' Syndrome.*—If, as we contend, these terms represent the initial and final phases of one and the same disease, why is it that most observers of the "irritable heart of soldiers" report such transitions but rarely? Rothschild (60) and Boas (61) did not see a single instance. There are a number of explanations for this discrepancy: 1) That the diagnosis was based upon the absence of clinical data rather than on their presence—data which became manifest only in the later stages of the disease. Persons with frank cases of Graves' syndrome were usually not inducted into military service, and when, by chance, they were, they probably were excluded from study. Graves' syndrome was common enough in World War I, both in military and civilian circles (28, 62–67), but, as far as we are aware, no study of this disease from the dynamic viewpoint was made. 2) There was insufficient follow-up. The only such study of neurocirculatory asthenia that is available is Grant's (68), who reported the follow-up of 665 patients who had been observed in the Colchester Camp for the study of the effort syndrome. None developed Graves' syndrome. This is hardly surprising in view of the fact that they had been noncombatants and the war had ceased. This leads to the third explanation. 3) That the malady lost its momentum because the stimulus, fear, was eliminated by the cessation of the war, and protective mechanisms (institutionalization) were invoked. This factor is, by all odds, the most likely. As circumstantial evidence, we cite again the statement of Cohn (36), who, in the week after that armistice, found neurocirculatory asthenia rare, whereas it had previously been common; in addition, we wish to call attention to the sudden diminution of articles on neurocirculatory asthenia in the *Index Medicus* after the cessation of hostilities, and the sudden rise with the onset of World War II. Curiously, nearly all of the reported cases in which such transitions were noted are in the literature concerning neurocirculatory asthenia in civil life (18, 50, 53, 56), which can only mean that these observers were in a better position to recognize transitions.

The following eleven cases, observed in the Mt. Sinai Hospital during the past eight years, are reported. In our opinion, the number of cases is significantly large when we consider that they occurred in a hospital where transitions perforce cannot be observed as frequently as in private practice. The number is too large to be subject to the mere law of chance. We would undoubtedly have been able to report many more instances of transition had we been less rigid in our interpretation of the previous history, in which, although the clinical evidences of neurocirculatory asthenia were patent, basal metabolic readings were unavailable. The main reason transitions are not more frequently seen is the

protection that envelops the patient as soon as the diagnosis of neurocirculatory asthenia is made. He is more or less shielded from, and rendered less amenable to, tribulation.

## REPORT OF CASES

H. L. (Adm. No. 374074) was admitted to the hospital in December, 1934, with a well-defined Graves' syndrome. She had been under the observation of one of us since 1925 because of classical neurocirculatory asthenia. She had been very "nervous throughout her youth, and, with the advent of adolescence, was subject to frequent crying spells, baseless apprehension, and frequent attacks of palpitation. She married at 23 years but her husband's long absences and suspected infidelities increased her instability. The birth of her only child, when she was 25 years old, brought complete absorption, with some recession of her symptoms. When, however, the child was old enough to go to school the enforced loneliness brought a marked exacerbation of the palpitation, sweats, and breathlessness. When first seen by us she presented a flushed facies, a very labile pulse rate and blood pressure, extreme hyperreflexia, and a marked anxiety state. Aside from its rapidity, the heart disclosed no abnormality; no murmurs were audible and the electrocardiogram was negative. There was slight, diffuse enlargement of the thyroid. The basal metabolic rate ranged from minus 10 per cent to plus 8 per cent. Sedatives and superficial psychotherapy, with some degree of cooperation on the part of the husband, brought temporary improvement. She was admitted to the Sydenham Hospital in June, 1931, where all investigations were negative and the basal metabolic rate was minus 6 per cent. With sedatives and rest in bed, the pulse rate became stabilized at 70. She was discharged with the diagnosis of neurocirculatory asthenia. In the latter part of 1933, she was deserted by her husband, and was forced to go on relief. Loss of weight, increasing nervousness, bulimia, increase in the size of the thyroid, and intense intolerance to heat appeared. She then presented the picture of Graves' syndrome, with exophthalmos, tremor of the fingers, a persistently rapid pulse, increased pulse pressure, and a markedly enlarged thyroid gland. The basal metabolic rate was plus 55 per cent. She was admitted to the Mt. Sinai Hospital in December, 1934, and had several brief attacks of paroxysmal auricular fibrillation during treatment with iodide. A two-stage subtotal thyroidectomy was performed, and the histologic appearance was that of a "follicular colloid adenoma with areas of hyperplasia." The symptoms and signs ascribable to the Graves' syndrome subsided rapidly. The emotional instability, pulse lability, and breathlessness are still present, with prompt accentuation under stress. The basal metabolic readings have remained normal until the present time (December, 1942).

W. McD. (Adm. No. 388170), a 30-year-old, married, billing clerk, was admitted to the Mt. Sinai Hospital Dec. 26, 1935, complaining of precordial oppression, nervousness, palpitation, and fatigability which, although present since early youth, had in the preceding eight months become considerably increased; additional recent symptoms were tremor, bulimia, and a loss of 20 pounds in weight.

He gave the following personal history when he first consulted the referring physician in 1928. He was the only child of apparently totally mismated parents, and his mother was twelve years his father's senior. His childhood was very unhappy; his mother was totally unsympathetic and manifested her resentment of him in a great many ways. The care of his father, who was rapidly becoming blind, fell entirely on the boy. At 13 years of age, after a rapid succession of conflicts at home, he first noted breathlessness, pounding of the heart, and nagging precordial sensations. He attended a commercial high school, but was compelled to leave six months before graduation and find a job, because his father was no longer employable. He became a bookkeeper in an uncle's business, but keenly felt his inability to complete school. He hated his work and even minor responsibilities produced

a sense of panic. Constantly criticized and frequently berated by his uncle, the attacks of breathlessness and palpitation became more frequent. A love affair, at 22 years of age, was finally terminated by the girl's parents after several years because of religious differences; her marriage, shortly thereafter, to another induced a profound and prolonged depression; he became totally disinterested in his surroundings. The cardiac symptoms increased in severity, and for several months he did not venture from his home. A physician assured him that he had no evidence of heart disease, and suggested rest in the country, which brought temporary improvement. Repeated basal metabolism measurements ranged from minus 10 per cent to plus 6 per cent. He then secured a position as a billing clerk, which he still holds. He has since condemned himself bitterly for not having left his family sooner. At 28 years he married, after a brief courtship, but it brought him neither kindness nor understanding. Within the first year of marriage his mother died of gangrene of the extremities, his father committed suicide, and his wife bore a child which she did not want. The discord which marked his marriage abetted his sense of inadequacy. His sexual adjustment was poor.

About eight months before entering the hospital, his symptoms increased, palpitation became almost constant, intolerance to heat became pronounced, there was a marked tremor of the fingers, and he lost 20 pounds in weight despite the fact that he maintained his appetite. On examination he presented the classical picture of Graves' syndrome. He was hyperkinetic and asthenic. There were a distinct stare, moderate exophthalmos, and a fine tremor of the fingers. The pulse rate, although labile, rarely fell below 100 beats per minute. A distinct bruit and thrill were present over the diffusely enlarged thyroid. The heart sounds were dynamic; the systolic blood pressure was 146, and the sounds were audible down to 0. The skin was moist, the palms were warm, and there was a marked tache. Thrills were felt along the larger peripheral vessels. The basal metabolic rate was plus 59 per cent, but fell after treatment with iodide, to plus 22 per cent within ten days. Thyroidectomy was performed, with the removal of at least seven-eighths of each lateral lobe. The postoperative course was smooth, and, on discharge, the basal metabolic rate was plus 2 per cent and the blood pressure was 120/76. The pathologic specimens disclosed "(1) hyperplastic thyroid, as seen in Graves' disease, and (2) a small piece of parathyroid and thymic tissue."

He was observed at frequent intervals until the present time (November, 1942). Although the symptoms and signs of Graves' syndrome have completely disappeared, he reverted to the status preceding the onset of thryotoxicosis. Emotional instability persists, as well as the cardiac sensations, tachycardia, flushing, apprehension, and hyperhidrosis; fatigability on even slight effort is pronounced. Repeated measurements of the basal metabolic rate have been normal.

D. F. (Adm. No. 406769), a 47-year-old housewife, was admitted to the hospital April 7, 1937, with a history of extreme nervousness since early youth. Vague precordial oppression, dyspnea, and palpitation would appear under any emotional stress. In the preceding ten years, her nervousness and excitability had increased considerably. About ten months earlier the patient had witnessed a robbery, which produced an hysterical state, with recurrent phobias and anxieties; she was compelled to remain in bed for several weeks. Crying spells were frequent. The events surrounding the robbery constantly reverted to her mind. She had been followed for several years in the surgical and medical clinics, and repeated examinations, including basal metabolic readings, were negative. Because of trembling of the right arm of four months' duration, Parkinsonism was considered, and she was admitted to the Neurological Service.

On examination, she was short and squat. The neurologic status proved to be entirely normal, and the trembling of the right arm, which soon disappeared, was interpreted as a manifestation of conversion hysteria. There was a firm, grape-sized nodule in the right lobe of the thyroid. The pulse rate was 68; the blood pressure was 130/80. The heart

disclosed no abnormality. She presented a flushed facies, mottling of the neck and chest, and marked sweating of the hands and feet.

After her discharge from the hospital, she was carefully followed, and the anxiety state persisted; any emotional crisis would precipitate breathlessness, precordial oppression, sweating, and palpitation.

In November, 1938, she began to lose weight, her appetite increased, and her previous symptoms were accentuated. The death of her mother, after thyroidectomy, shortly before her readmission to the hospital, on May 8, 1939, added to her apprehension. On examination she presented a well-defined Graves' syndrome, with exophthalmos, marked bilateral tremor of the fingers, persistent tachycardia, bulimia, and a weight loss of 22 pounds. Urinary frequency and diarrhea were pronounced. The basal metabolic rate was plus 46 per cent. With iodide treatment, the pulse rate fell from 120 to 70 and the basal metabolic rate to plus 14 per cent. Subtotal thyroidectomy was performed seventeen days after admission, and histologic study revealed a "hyperplastic thyroid with areas of colloid, as seen in Graves' disease." The thyrotoxic symptoms rapidly subsided after operation. She was not followed thereafter.

L. H. (Adm. No. 441026), a 40-year-old German refugee physician, was admitted to the hospital May 6, 1939, with Graves' syndrome. During the preceding five months there had been increasing enlargement of the neck, a loss of 30 pounds in weight, extreme nervousness, tremor, palpitation, and bulimia.

Since early youth, he had been very introspective, easily frightened, and apprehensive. In high school he would experience violent palpitation and dyspnea when called upon to recite or during examinations. He was told that, when frightened, his skin would assume a subicteric hue. With the advent of the Hitler regime his symptoms became more pronounced, with almost constant palpitation, precordial oppression, fatigability, and irritability. Holidays and sedatives would bring transient relief. The basal metabolic rate was normal on several occasions.

On examination he was hypermotile, and there were a distinct stare and lid-lag. The left lobe of the thyroid was enlarged to the size of a lemon. The heart rate varied from 96 to 110 beats per minute. The blood pressure was 146/68. The spleen was enlarged 2 fingerbreadths below the free border of the ribs. A chest roentgenogram disclosed moderate extension of the thyroid into the left upper part of the mediastinum. The basal metabolic reading on admission was plus 40 per cent, and fell to plus 12 per cent after nine days of treatment with iodide. Subtotal thyroidectomy was performed, and histologic examination disclosed a hyperplastic thyroid, as seen in Graves' disease. The postoperative course was uneventful.

The picture of neurocirculatory asthenia has not, however, been significantly altered, and he still responds to difficult situations with palpitation, precordial oppression, fatigability, and, at times, dyspnea.

Mrs. B. B. (Adm. No. 414655), a 59-year-old mother of two children, came under our observation in 1924, at the age of 41. She complained of a peculiar aching sensation in the precordium, palpitation, hyperhidrosis, and apparently baseless crying spells. Similar symptoms had been present since early childhood. She recalled that, when her father died suddenly when she was 6 years old, her mother made a constant companion of her, and she was subsequently entrusted with most of the household duties and care of the other children. These responsibilities often engendered a sense of inadequacy and panic, accompanied by trembling, sweats, and pounding of the heart. She would weep because of fancied slights, a tendency which persisted even after what was apparently a very happy marriage. Frequent examinations never disclosed any evidence of disease. The hands were constantly moist, cool, and bluish; the resting pulse rate was 72, and the basal metabolic rate varied from minus 10 per cent to plus 5 per cent. Her blood pressure fluctuated widely; it would reach 160/100, but promptly fall to normal on recumbency. When any member of her

family fell ill her symptoms would multiply, with almost constant palpitation, precordial oppression, and dyspnea. A small thyroid adenoma appeared after the birth of her second child, when she was 24 years old, but never seemed to increase in size. Repeated cardiovascular studies failed to disclose any evidence of disease. The advent of the menopause at 49 years somewhat accentuated her vasomotor instability.

In October, 1926, she began to lose weight in spite of a tendency to bulimia. The heart rate rarely fell below 110, even during sleep, and the pulse pressure rose. A slight stare and lid-lag appeared. The basal metabolic rate was plus 48 per cent. In deference to her dread of operation, palliative measures were instituted, with temporary remission of symptoms, and the basal metabolic rate fell to plus 24 per cent. This was only transient, however, and, with the return of a severe Graves' syndrome, subtotal thyroidectomy was performed Oct. 6, 1937. The postoperative course was uneventful, with rapid diminution of the nervousness, hyperactivity, tremor, tachycardia, and bulimia. She promptly regained her lost weight.

During the last five years she has been under careful supervision, and there has been no return of the Graves' syndrome. The emotional instability and other symptoms identified with the neurocirculatory asthenia that she manifested prior to the appearance of the hyperthyroidism persist unchanged.

T. L. (Adm. No. 430214), a 35-year-old housewife, was admitted to the hospital (Dr. Baehr's service) Sept. 29, 1938, at which time a diagnosis of neurocirculatory asthenia and anxiety neurosis was made. She had always been intensely sensitive, and had been subject to attacks of weakness, breathlessness, and palpitation since adolescence. At the age of 24 years, shortly after the birth of her second child, she had a severe "nervous breakdown," and was in bed for a month. Profound weakness, persistent palpitation, and hyperhidrosis persisted until she secured relief after a sojourn in the country. During the preceding four years, palpitation became more frequent, and appeared after but slight strain and lasted as long as three hours. The attacks began suddenly, with irregular pounding of the heart and frequent sharp precordial pain radiating to the interscapular region. In the intervals between attacks, she was unable to concentrate. She experienced generalized body tremors and was asthenic. There were also recurrent attacks of dyspnea, suggesting "sighing respiration," which were unrelated to the palpitation, and appeared chiefly when she was at rest. Diffuse sensations of warmth, followed by profuse sweating and chills, occurred several times daily. Excitement or fear, induced by trifling incidents, would precipitate severe diarrhea. Repeated measurements of her basal metabolic rate, made largely at the insistence of the patient because her mother had had Graves' syndrome, ranged from minus 10 per cent to plus 12 per cent. On examination she was somewhat apathetic. There was no exophthalmos or lid-lag. There was no tremor of the fingers. There was slight, diffuse enlargement of the thyroid. The pulse rate was labile, varying from 110 to 68. The heart sounds were loud and booming. The basal metabolic rate was plus 5 per cent. Psychiatric consultation disclosed the fact that she was an emotionally immature person who was almost completely dependent on her mother in spite of her marriage of eighteen years. She had never quite recovered from the trauma of her mother's death four years before. It was felt that there was a distinct psychogenic coloration to the attacks of dyspnea and palpitation, for they subsided promptly when she was relieved of her household responsibilities. Further observation in the hospital failed to disclose any evidence of organic disease. The pulse rate became slow, the tremor disappeared, and there was no heat intolerance. Subsequent basal metabolic readings varied from plus 12 per cent to minus 10 per cent.

After her discharge from the hospital there was some amelioration of her symptoms; she gained weight and the attacks of tachycardia and breathlessness diminished both in frequency and intensity. She was carefully observed in the Out-Patient Department, and appeared to respond well to superficial psychotherapy. In the light of her patently improved status, the case was finally closed in January, 1940.

In June, 1940, almost immediately after a severe nervous shock, the nature of which she refused to disclose, her diarrhea returned and she had as many as eight movements a day; palpitation, precordial pain, intense nervousness, and an inordinate increase in appetite and extreme weakness appeared. The basal metabolic rate was plus 36 per cent. On readmission to the hospital on Aug. 16, 1940, she presented marked exophthalmos, tachycardia, with a constant rate of 110, extreme nervousness, and a blood pressure of 160/90. It was felt by the staff that she had Graves' syndrome, and, after preliminary iodide treatment, with a fall in the basal metabolic rate to plus 3 per cent, a subtotal thyroidectomy was performed. The resected gland was reported as "hyperplastic thyroid, as seen in Graves' disease in a colloid phase." The thyrotoxic symptoms diminished rapidly after operation.

She has been followed at intervals of a few months until the present time. Although she has gained twelve pounds in weight and the tremor, bulimia, and pulse rate lability have disappeared, the heart consciousness, sighing respiration, and precordial awareness persist.

R. S. (Adm. No. 434778), a 36-year-old housewife, came under the observation of one of us in 1934, complaining of nervousness, palpitation, fatigability, and sweating, particularly under emotional stress. Although these symptoms had been present to a variable degree since adolescence, economic reversals after marriage and the care of two children with behavior problems accentuated her instability. In early youth she had several attacks of syncope, induced by either pain or fright. Two attacks of rheumatic fever, the first at 15 years and the second at 26 years, necessitated many months in bed, but there was no complicating valvular disease. Repeated assurance that her heart was not affected scarcely diminished her apprehension and introspection. On examination, she presented a flushed facies and mottling of the neck and chest. The heart rate was labile and the sounds dynamic. The blood pressure was 118/84. The palms were cool and moist. Fluoroscopically, the cardiac configuration was normal, and the electrocardiogram was negative. The basal metabolic rate was minus 8 per cent. She was seen on several occasions in the next three years without any change in the clinical picture except for rapid improvement during vacations; the basal metabolic rate remained below normal. Therapy was limited to suggestion, reassurance, and sedatives.

About six months preceding admission, her husband's refusal to consider having another child led to an estrangement. Her symptoms rapidly increased, palpitation became almost constant, enlargement of the neck appeared, and, despite increased appetite, she lost 10 pounds in four months.

She was admitted to the hospital Jan. 11, 1938, with a classical Graves' syndrome. There were distinct exophthalmos, tremor of the fingers, hypermotility, a diffusely enlarged thyroid, and a basal metabolic rate of plus 44 per cent. The heart rate rarely fell below 110 beats per minute. The blood pressure was 156/84. The electrocardiogram disclosed the prominent P and T waves of Graves' syndrome. The palms were warm and moist. With iodide treatment the basal metabolic rate fell to plus 12 per cent, and a subtotal thyroidectomy was performed. Histologic examination disclosed a "hyperplastic thyroid, as seen in Graves' disease." The postoperative course was smooth, and the symptoms of hyperthyroidism subsided rapidly.

She has been seen at four-month intervals. The basal metabolic rate has varied from minus 12 per cent to plus 4 per cent. Although she has had a complete reconciliation with her husband, the nervous instability, intermittent palpitation, fatigability, and heart consciousness that she manifested before the onset of the Graves' syndrome persist without significant change.

R. A. (Adm. No. 453642), a 25-year-old, married schoolteacher, consulted one of us in January, 1937, because of recurrent attacks of breathlessness, precordial oppression, palpitation, nervousness, and sweating. Nervous instability and intermittent anxieties had

been pronounced since early childhood; she had been taken to numerous physicians who succeeded only partly in assuaging her fears that her heart was diseased and that death was imminent. Sighing respiration persisted through adolescence, but diminished when she was married at the age of 19 years. With the advent of pregnancy, 3 years before, all of her earlier symptoms returned with great intensity, but were abruptly terminated by the birth of a normal child. In the next two years, however, her child's many illnesses, a very difficult school class, and her husband's loss of his position induced a severe exacerbation of her instability. In spite of a diminished appetite, her weight remained stationary. On examination, she appeared well nourished but extremely apprehensive, and showed a well-defined autonomic imbalance. The pulse rate varied from 150 to 90; the palms were cool and moist; there was moderate, diffuse fullness of the thyroid; the heart sounds were dynamic, and the deep tendon reflexes hyperactive; the basal metabolic rate was minus 6 per cent. In spite of reassurance, persuasion, and sedatives, her symptoms persisted, presumably because of increasing economic burdens and the severe illness of both her parents. Paroxysms of tachycardia, with the heart rate reaching 160 per minute, were precipitated by even mild irritation. These attacks were often promptly terminated by her physician's reassurance. Measurements of the basal metabolic rate, which were made frequently, largely because of the patient's insistence, varied from minus 10 per cent to plus 4 per cent.

In January, 1940, weight loss became evident, her appetite suddenly increased, and the resting pulse rate, which was previously about 70, rarely fell below 100. A distinct stare and a fine tremor of the fingers appeared. In the space of six weeks she lost 12 pounds and noted extreme intolerance to heat. The basal metabolic rate was plus 32 per cent. There had been amenorrhea for two months. There was a marked skin tache, and the palms of the hands, previously cold and moist, became quite warm. The thyroid had enlarged considerably and was firm. She became pregnant in February, 1940, and was admitted to the Mt. Sinai Hospital March 12 for a therapeutic abortion because of active Graves' syndrome. A few hours after admission she aborted spontaneously. Iodide treatment was begun one week thereafter, and a subtotal thyroidectomy was performed April 6. Histologic study of the resected gland disclosed "hyperplastic thyroid, as seen in Graves' disease in the colloid phase." Convalescence was uneventful, and she was discharged to a rest home a week later.

She has been seen at frequent intervals since her discharge from the hospital. The basal metabolic rate is persistently normal. Although she presents none of the residua of the Graves' syndrome, the emotional lability, unstable pulse rate, heart consciousness and hyperhidrosis persist.

S. S. (Adm. No. 456692), a 45-year-old German refugee housewife, was admitted to the hospital May 14, 1940, and, after a week's observation, diagnoses of neurocirculatory asthenia, anxiety neurosis, psoriasis, and a possible anginal syndrome were made. She had been nervous since childhood, and had responded to difficult situations with palpitation and sweating. Dyspnea on exertion was first noted five months before admission, and was accompanied by mild precordial pain. Since coming to this country she had been compelled to do domestic work in addition to taking care of her own household. She was greatly concerned over a brother who was stranded in Europe. On examination she presented a moderately labile, variable pulse rate. A soft systolic murmur was audible over the pulmonic area. The edge of the liver was felt one fingerbreadth below the costal margin. There were many scattered psoriatic lesions on the skin. Several basal metabolic readings varied from plus 4 per cent to minus 10 per cent. Psychiatric consultation indicated that anxiety played the dominant role in her illness. She was approaching the menopause, was burdened with the usual problems besetting refugees, and she worried lest she develop Graves' disease, as her mother had done. The heart did not show any evidence of disease.

After her discharge from the hospital she showed moderate improvement for several weeks. Further psychic trauma, however, soon induced a return of all her former symptoms, with such additional complaints as an increased desire for food, persistent palpitation,

constant nervousness, prominence of the eyes, and enlargement of the neck. She was readmitted to the hospital Aug. 20, 1940, with the unmistakable picture of Graves' syndrome. The basal metabolic rate was plus 54 per cent. The thyroid was diffusely enlarged. A loud systolic murmur was audible over the entire precordium. The blood pressure was 154/70. After fourteen days of iodide treatment, the basal metabolic rate fell to plus 9 per cent, and a subtotal thyroidectomy was performed. The pathologic report was "hyperplastic thyroid, as seen in Graves' disease in the colloid phase."

Although disappearance of the thyrotoxic symptoms was rapid, the emotional instability was not significantly affected. Intermittent palpitation, flushing, and fatigability varied with the degree of her economic and social stability. She was readmitted to the hospital Jan. 6, 1941, for the removal of a lipoma of the breast. She presented a well-defined picture of neurocirculatory asthenia. The basal metabolic rate was minus 6 per cent.

H. F. (Adm. No. 458510), a 48-year-old married tailor, was admitted to the hospital Aug. 18, 1940, with the classical picture of Graves' syndrome. He first consulted one of us in March, 1934, at which time he complained of extreme nervousness, palpitation, sweating, fatigability, and aching precordial sensations, chiefly when under emotional stress. Two nervous breakdowns within the preceding five years induced prolonged incapacity. Marked nervous instability had been present since early youth. His environmental adjustments had been uniformly poor. His mother died in an institution for the insane, and he constantly dreaded a similar fate. He had never been able to earn a satisfactory livelihood. For more than eight years, he and his wife lived in furnished rooms and ate in cheap restaurants. During his "slow" seasons his symptoms diminished, only to be aggravated when he was compelled to work hard.

When first seen he presented a flushed facies, labile pulse rate, and hyperhidrosis; the examination was otherwise negative. The basal metabolic rate was minus 4 per cent. He was considered to be suffering from neurocirculatory asthenia, and was treated with reassurance, encouragement, and sedatives, occasionally. Improvement was variable, but he responded, as a rule, to superficial psychotherapy. He was seen at frequent intervals in the following six years, during which there was but little change in the clinical picture. Several basal metabolic readings were normal.

About eight months preceding admission he sustained a severe nervous shock, which was soon followed by a distinct change in his symptoms. Nervousness and palpitation became constant, a poor appetite was replaced by actual bulimia, he lost 15 pounds in weight, and intolerance to heat became pronounced. Substernal pain was induced by even mild exertion. On admission, he presented a distinct stare and lid-lag. The heart rate was 124 beats a minute. A plum-sized adenoma of the left lobe of the thyroid was continuous with a substernal extension, as revealed by roentgenogram. A harsh systolic murmur was audible at the apex. The basal metabolic rate was plus 32 per cent. With iodide therapy the rate fell to plus 10 per cent, and a subtotal thyroidectomy was performed. Histologic study of the resected gland disclosed a "hyperplastic thyroid, as seen in Graves' disease." Improvement after operation was very rapid, with prompt disappearance of the hyperthyroid symptoms. There has been no change, however, in the underlying neurocirculatory asthenia.

H. B. (Adm. No. 459771), a 40-year-old retail shoe dealer, entered the hospital July 13, 1940, with the classical picture of Graves' syndrome. He stated that he had been highly impressionable and sensitive since early childhood, rarely entered into the activities of his schoolmates, and was largely asocial. Shortly after his marriage, eight years before, nervousness and irritability became more pronounced. Attacks of emotional instability, accompanied by pounding of the heart, precordial oppression, and moderate dyspnea were precipitated by even minor conflicts or irritations; constipation was pronounced. He was studied by several physicians, but failed to find comfort in their negative examinations. Repeated basal metabolic readings were normal. In the preceding four years his com-

plaints were persistent. In the last year, however, longstanding, stubborn constipation was replaced by a tendency to frequent and loose evacuations. Three months prior to admission to the hospital, he took over the added responsibilities of a larger business which necessitated gruelling work and long hours. He then noted rapid weight loss, persistent palpitation and dyspnea on but slight exertion, increasing nervousness, and enlargement of the neck. Prominence of the eyes had been but recently noted. The basal metabolic rate was plus 54 per cent.

On examination, he was hyperactive, with a distinct tremor of the fingers, a resting pulse rate of 110, a marked stare, and enlargement of the left lobe and isthmus of the thyroid. Aside from the tachycardia, cardiovascular studies were negative. Psychiatric investigation disclosed a frustrated, unhappy man, profoundly depressed by his insecurity and illness. With iodide therapy and sedatives, the basal metabolic rate fell from plus 46 per cent to plus 18 per cent, and a subtotal thyroidectomy was performed. Histologic study of the resected gland revealed a "hyperplastic thyroid, as seen in Graves' disease in the colloid phase."

He has been seen subsequently at frequent intervals. Although the basal metabolic readings have been consistently below normal (minus 4 per cent to 10 per cent), and there are no residual signs of the Graves' syndrome, the nervousness, palpitation, and dyspnea that he had experienced for many years preceding the onset of the disease have persisted without interruption.

SUMMARY

All evidences point to the psychosomatic nature of neurocirculatory asthenia. Neurocirculatory asthenia is by no means a disease incidental to war, and it is more common in women than men. Viewed from the dynamic and biologic aspects of Graves' syndrome, the similarity between neurocirculatory asthenia and the initial or larval phase of Graves' syndrome is so close that we believe the two are identical. Transitions of neurocirculatory asthenia to Graves' syndrome and the reverse are by no means uncommon. Eleven such instances are reported.

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CHAPTER 12

# TOXIC HEPATITIS

Toxic hepatitis or infectious hepatitis is conventionally classified into two forms, "catarrhal icterus"[1] and "acute yellow atrophy" with the implication that they are two separate and distinct diseases, the main distinction being that in "catarrhal" icterus, the patient recovers while in acute yellow atrophy the patient dies. This distinction, however, is not valid because occasionally "catarrhal icterus" passes imperceptibly into "acute yellow atrophy" with fatal outcome and on the other hand, cases of "acute yellow atrophy" may recover. Such transitions lead one to suspect that the two diseases are identical, and this is confirmed by their morphologic identity. In the few autopsies that have been reported on patients who have died by accident with what appeared to be clinical "catarrhal icterus", degeneration of the liver with focal areas of necrosis were found, precisely, similar to those witnessed in the early phases of acute yellow atrophy (Eppinger (1), Klemperer, Kilian and Heyd (2)). Indeed, these observers hold that "catarrhal icterus" is identical with acute yellow atrophy differing only in degree. Eppinger calls catarrhal icterus "acute yellow atrophy en miniature." Moreover the two diseases possess clinical similarities. For instance, in both there is a lowered cholesterol and cholesterol ester in the blood (Ottenberg and Spiegel (3)), and the tyrosinuria, which formerly was regarded as pathognomic for acute yellow atrophy is found by the more delicate methods devised by Lichtman and Sobotka (4) in many cases of "catarrhal icterus." The galactose test for liver function which indicates more or less quantitatively parenchymal damage is more frequently positive in catarrhal icterus and acute yellow atrophy than in any other hepatic disorders (Ottenberg and Spiegel (3)). Finally, the epidemiologic incidence between the two diseases is identical (Bergstrand (5)).

In the acute phases of toxic hepatitis, therefore, a wide variety of clinical manifestations are observable varying from a mild form with complete recovery to that conventionally described under the heading of "acute yellow atrophy" ending in death from cholemia or from the so-called hepato-renal syndrome.

[1] "Catarrhal" icterus is probably not a single disease, but a syndrome, the result of various morphologic backgrounds. We are not referring to cases due to a swelling of the papilla of Vater due to a gastroduodenitis or to a cholangitis.

Most cases of "catarrhal" icterus, therefore, are potentially acute yellow atrophies.

If the patient survives, regeneration arising from the intact areas of hepatic parenchyma ensues, which, depending upon the extent of destruction and of survival of the parenchyma, may vary from slight connective tissue replacement with slight or moderate compensatory hypertrophy of the remaining liver lobules to extensive band-like infiltration of connective tissue and the formation of compensatory adenomatous-like masses throughout the liver. These represent end results and have received different eponyms, e.g., "toxic cirrhosis" (Mallory (6)), "nodular sclerosis," "nodular hyperplasia" and "multiple adenomata of the liver." The clinical expression of toxic hepatitis does not always parallel the morphologic, as evident from the observation that not infrequently the patient dies early in the course of the disease, while at autopsy the subacute or chronic stage is found. This proves first, that the malady is sometimes dormant long before the clinical manifestations appear. This was shown by English observers in World War I, when it was noted that in workers in trinitrotoluene, the disease manifested itself weeks and sometimes months after cessation of contact (Rolleston (7)); and second, that the regenerative power of the liver is enormous and death usually comes only when there is not sufficient normal hepatic tissue to carry on adequate function.

It matters not what the cause of the toxic hepatitis may be; whether it is known, as for instance, phosphorus, chloroform, carbon tetrachloride, mushrooms, syphilis, salvarsan, etc. or unknown. In all, the lesions resemble those of acute yellow atrophy so closely as to be practically indistinguishable. Furthermore, the anatomic end-results are alike.

Whether a complete anatomical restoration to normal occurs in toxic hepatitis is doubtful; as in cases of acute glomerulonephritis, the earliest healed phase is unknown. That complete anatomic recovery does not in all likelihood occur is shown by Soffer and Paulson (8) who, using the bilirubin excretion test in eleven patients who had toxic hepatitis several years previously, found that in nine there was a retention of between 10 to 50 per cent at the end of four hours. Between this early phase, which gives little or no clinical manifestations and the terminal, designated by such terms as toxic cirrhosis, nodular sclerosis, nodular hyperplasia, etc. gradations in clinical severity accompanied by various degrees of morphologic changes occur depending in all probability, as previously noted, upon the extent of initial destruction and the capacity for regeneration. This intermediate phase is termed "subacute" or "red atrophy of the liver."

In the vast majority of instances, as far as morphology is concerned, the biological course is complete when toxic cirrhosis, nodular hyperplasia, etc. are produced.

The fate of the patient depends largely upon the extent of the damage and the degree of regeneration. If the expression of the disease has been mild, the patient may reveal nothing clinically but an enlarged and perhaps irregular liver and an enlarged spleen, and he eventually succumbs to a totally unrelated malady. If severe, he may die from progressive hepatic insufficiency with jaundice and

cholemia or he may develop, as in other forms of cirrhosis, hypertension of the portal circuit with ascites, etc. In some instances, for unknown reasons, a recurrence of an acute hepatitis arises which rapidly results in death.

Whether carcinoma ever arises in such a liver is problematic because I have not been able to find a case in which such a transition was noted. That carcinoma arises in cirrhotic livers is well admitted, accounting for the majority of reported primary carcinomata of the liver, and the carcinomata of the liver arising in Chinese affected with clinorchis sinensis causing secondary hepatic cirrhosis.

### The Biology of Toxic Hepatitis

Toxic hepatitis → acute yellow atrophy → { acute cholemia: / hepato-renal syndrome } → recovery → toxic cirrhosis (synonyms)

( Synonym: catarrhal icterus )

{ acute cholemia: / hepato-renal syndrome } → death

recovery → toxic cirrhosis (synonyms):
- nodular cirrhosis
- compensatory adenoma
- nodular hyperplasia
- chronic infectious jaundice

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CHAPTER 13

# LAENNEC OR PORTAL CIRRHOSIS

While the distinction between toxic hepatitis or portal cirrhosis is sometimes not always possible, portal cirrhosis differs from toxic hepatitis in the following respects: 1. In portal cirrhosis the process is diffuse and evenly distributed. In toxic hepatitis, sometimes considerable areas of the parenchyma are intact and the portions of liver involved are irregular in distribution. 2. In portal cirrhosis there is a genuine hyperplasia of connective tissue. In toxic hepatitis the connective tissue represents, to a large extent at least, a condensation of the fibrous framework of the organ (1). 3. Etiologically the evidence is very strong, as we shall try to show, that portal cirrhosis is in large part a deficiency disease. Toxic hepatitis, both clinically and experimentally, is caused by poisons; chloroform, trinitrotoluene, arsenic, carbon tetrachloride, phenylhydrazine, phosphorus, cincophen, salvarsan, etc. Also judging from recent investigations on acute infectious hepatitis in World War II (2) the probability is strong that a filtrable virus is sometimes involved. 4. Most important of all the biology of the two diseases is entirely different. We have already reviewed the biology of toxic hepatitis in Chapter 12. We will now review the biology of portal cirrhosis.

A. *The etiology of portal cirrhosis.* The relation of alcohol to the production of cirrhosis was for long misunderstood, largely because experimentally it was impossible to reproduce portal cirrhosis by alcohol alone. This observation together with the fact that portal cirrhosis occurred frequently in the proven absence of alcoholism, led some to seriously question the causal relation of alcohol to cirrhosis. Nevertheless the high incidence of a history of alcoholism in portal cirrhosis (3 and 4), its frequency in certain occupations in which easy access to alcohol is available (e.g. brewery employees and bartenders) and the decline and rise of portal cirrhosis in this country following prohibition and its repeal (1), cannot be ignored. Thanks largely to the work of Connor (5) and to recent experimental investigation, the causal relation of alcohol to portal cirrhosis is slowly being clarified. Its action is not direct but an indirect one.

It has long been known that alcohol addicts have a deficient food intake. Romano (6) in a study of 131 chronic alcoholics found that nearly a half were on a deficient diet. Of these 79 per cent had a polyneuritis. This accords with the frequent history of polyneuritis due to thiamin deficiency antedating cirrhosis of the liver (7 and 8). The diet is apt to be limited to proteins and fats with

little carbohydrate, and poor in certain vitamins especially vitamin B (5). The reasons for the deficient food intake are the following: 1. The high caloric value of alcohol which spontaneously decreases the need for additional food calories. 2. The loss of appetite through thiamin deficiency and in some instances to an alcoholic gastritis. The frequency of achlorhydria in alcoholics has been stressed (4). In the past few years successful experimental reproduction of portal cirrhosis has been accomplished by various types of deficient diets, and although no unitary mechanism has as yet been forthcoming, these results help to clarify much of the obscurity of the pathogenesis of portal cirrhosis and particularly the etiological relation of alcohol.

Chaikoff, Conner and Biskind (9) kept depancreatized dogs treated with insulin alive for 2.6 to 5.8 years and obtained fatty livers which eventually revealed the typical morphological appearance of portal cirrhosis. In the terminal stage the fat content of the liver returned to normal. They found the precise sequence noted in human cirrhosis, namely, fatty infiltration, hyaline degeneration, atrophy of the hepatic cells at the periphery of the lobules, and subsequent periportal fibroplastic proliferation, ending in the typical hobnailed liver. Later Chaikoff and Conner (10) fed dogs on a high fat diet and in three of four animals that lived between 138 and 386 days a fatty liver developed with fibrosis, but these livers differed from the preceding in that the fibrosis was diffuse and not perilobular. Gyorgy and Goldblatt (11) produced fatty infiltration with cirrhosis on diets deficient in vitamins $B_1$, $B_2$ and riboflavin. Later the same investigators (12) produced focal and diffuse hepatic necrosis with fatty infiltration followed by a portal cirrhosis, in rats in 100 to 150 days by a diet of moderately high or a high content of fat but low in casein and choline, both lipotropic factors. Cystine added to the diet aggravated the cirrhosis while supplements of choline reduced the severity and incidence. Methionine, another lipotropic factor, was highly effective in preventing injury. Furthermore these animals revealed effusions into the pleura, pericardium and peritoneum, sometimes even bloody; the effusions possessed a low serum albumin, between 1.5 and 2 per cent. Although the necrosis is central or midzonal the cirrhosis is periportal. Bollman (13) also found a diminution in blood serum protein in carbon tetrachloride poisoned animals and noted that ascites developed only when the serum albumin was low. Blumberg and McCollum (14) produced cirrhosis in rats with a high fat and low protein diet which could be prevented by choline. They also report an accentuation of the cirrhosis by adding cystine but found that the daily addition of 10–20 mgm. of choline or one gram of yeast or both neutralized more or less completely the effect of cystine on the liver. Rich and Hamilton (15) on diets supplemented by vitamins but lacking yeast produced a fatty liver with portal cirrhosis. They determined that the cirrhosis was not due to the lack of vitamins $B_1$, $B_2$, $B_6$, or nicotinic acid. They could prevent the cirrhosis by adding yeast.

Lillie, Daft and Sebrell (16) produced a fatty cirrhosis in the course of a year on a diet low in protein and low in the sulfur containing aminoacids. If alcohol is added the changes are more marked.

Earle and Webster (17) on a diet of which 10 per cent was cystine obtained a

cirrhosis preceded by a hemorrhagic necrosis resembling that observed in eclampsia and followed by fatty infiltration.

Halliday (18) on a basic diet of only 5 per cent fat and 73 per cent sucrose and deficient in vitamin $B_6$ produced a fatty liver which could be remedied to a large extent by choline.

Gavin and McHenry (19) by adding choline could prevent the development of a fatty liver on a vitamin B deficient diet.

Webster (20) produced fatty livers in rats on a diet poor in protein and choline and rich in fat, which could be prevented by a rich protein diet with the addition of molasses or yeast. The addition of cystine increased the severity of the process.

Fouts (21) produced fatty cirrhosis in dogs fed on a low protein diet supplemented by thiamin, riboflavin, nicotinic acid, pyridoxine and pantothenic acid. The administration of a high protein diet with casein prevented the process. Clinical improvement followed the ingestion of large amounts of choline or powdered liver extract. Evidences of vitamin deficiency disappeared but the fibrosis of the liver persisted.

Spellberg, Keeton and Ginsberg (22) obtained fatty livers and cirrhosis on a diet containing 20 per cent fat—chiefly butter fat. Other fats, for instance hydrogenated vegetable oil (Crisco) did not produce fatty livers, which leads them to believe that it is not fat alone but the kind of fat that impregnates the liver cells that causes damage.

Even in the experimental production of toxic hepatitis the destructive effects may be minimized or entirely neutralized by similar substances. Von Glahn and Finn (23) lowered the incidence of cirrhosis produced by lead arsenate by adding brewer's yeast to the diet. The effect is independent of the glycogen content. Miller, Ross and Whipple (24) gave animals almost complete protection from chloroform hepatic injury by administering methionine and/or, to a lesser extent, cystine before the anesthesia. Other nonsulfur containing aminoacids alone or in various combinations afforded no protection.

From these apparently diverse data these facts can be gleaned—a. That diets deficient in certain substances may produce cirrhosis. This deficiency may be either an unknown member of the vitamin B complex that is contained in brewer's yeast, or the absence of a lipotropic factor, of which the most active are choline, methionine and betaine. The lipotropic action of casein is due to the methionine cotent (25). Both are independent of the glycogenic function of the liver. Choline cannot exert its lipotropic action on a fatty liver due to a high fat diet, apparently because the fat is deposited too fast; nor does it act on all types of fatty liver; for instance it does not prevent a fatty liver from developing after tetrachloride poisoning, although it hastens the disappearance of the fat (25). The precise mechanism whereby lipotrotropic substances act is unknown. b. That the cirrhosis is almost in every instance preceded by a fatty change either with or without an accompanying necrosis. This holds true even when a cirrhosis is produced by toxic substances, for instance, phosphorus, carbon tetrachloride and chloroform. c. Protein deficiency alone does not cause

cirrhosis, for cirrhosis can even be induced experimentally on a high protein diet. Apparently, cirrhosis is determined by deficiency of certain amino acids in the protein content that are largely lipotropic in action (26).

As far as these experimental results permit us to say, apparently any method whereby a very prolonged and pronounced fatty infiltration of the liver is produced may in time induce portal cirrhosis of the liver. Fatty infiltration (not degeneration!) resulting from a high fat diet, the absence of a lipotropic factor in the diet or a deficiency in the vitamin B complex alone will not produce cirrhosis; an interaction of these factors is essential plus a sufficiently prolonged period. That a fatty infiltration of the liver represents the initial stage of a portal cirrhosis in human beings is fairly well acknowledged. Connor (5) who has had an unusual experience with alcoholism and cirrhosis describes three stages. The first stage is a fatty liver which develops after prolonged ingestion of large amounts of alcohol during which period little or no food is taken or food which contains protein and fats only. The liver is smooth and large. Because of swelling there may be intrahepatic obstruction of bile ducts with resulting jaundice. In the second stage, the liver is still fatty and larger than normal, but there is a progressive perilobular fibrosis. The liver in this stage may be smooth or slightly lobulated. If the individual lives long enough, the liver is reduced in size and nodular, and fat may or not be present. This change in morphology has been noted in biopsies taken years apart (27). The individual may die from an intercurrent infection or from "beri-beri" heart at any stage so that a pronounced fatty infiltration found at autopsy does not necessarily represent an end stage. It is problematical whether a fatty infiltration of whatever origin, given sufficient time, will eventually develop portal cirrhosis. Undoubtedly the quantitative factor, whether it is sufficient to compress and distort the parenchyma, is a necessary consideration, aside from the continuance of the factor that brought the fatty change about.

Human cirrhosis parallels experimental cirrhosis in its favorable response to a nutritious diet and vitamin B concentrate. Patek and Post (28) found that the survival period after two years of observation was greater than in controls and that the survival period after ascites developed was also greater than in controls. The vascular spiders may even disappear. Connor (5) has determined that an adequate diet plus alcohol will not give cirrhosis, and that in animals it is possible to maintain adequate metabolic equilibrium by proper diet even when large amounts of alcohol are given.

Obviously once new connective tissue has invaded an organ, a complete restitutio ad integram is not possible. Because the liver has enormous compensatory power, the influence of this new tissue upon the reduction of the parenchyma is probably not as serious as its compressing effect upon the finer portal radicles. McIndoe (29) by corrosion technique and Herrick (30) and Dock (31) by perfusion of human cirrhotic livers, have shown that the vascular supply and especially of the portal system is appreciably reduced, with consequent hypertension in the portal circuit. Rousselot, Thompson, Whipple and Coughey (32) have demonstrated such a hypertension in the living subject. Obviously,

the cure of portal cirrhosis lies in prophylaxis or at least in early recognition. Unfortunately, liver function tests in early stages do not always indicate the presence or degree of liver damage, so that one must depend on pure clinical observation. One awaits with interest mass data on the treatment of early portal cirrhosis by methods based on the prevention of experimental portal cirrhosis.

The relation between dietary deficiency and experimetal portal cirrhosis may serve as a possible explanation for the hitherto etiologically obscure non-alcoholic cases of portal cirrhosis. Suggestive in this connection is the high incidence of portal cirrhosis in natives of tropical countries (33, 34, 35 and 39) which has been conventionally ascribed to a highly spiced diet and to absorption of toxins. Rogers (36) in India found an incidence as high as 6.9 per cent; Tyagaraya (37) in Ceylon, 5.6 per cent, mostly among the poor classes. In the latter country the diet of the natives consists of rice, vegetables and dried fruit, and is lacking in nitrogen and certain vitamins. Wang (38) in Manchuria reports 54 cases, occurring mostly in the working classes and in farmers. Stitt (35) remarks upon the frequency of Laennec cirrhosis in the tropics, especially in the Dutch East Indies, Java and Sumatra. Malaria has often been ascribed as a cause of cirrhosis especially in tropical countries, but the evidence is entirely inconclusive (1). Ratnoff and Patek (4) believe that it is more likely that dietary deficiency has been disregarded.

Our understanding of the causal relation of dietary deficiencies to portal cirrhosis is so recent that the elucidation of a history of dietary deficiency has not been as yet practiced on a large scale, but Ratnoff and Patek (4) state that if delved into, such a history is usually found.

The reports of the rare causes of cirrhosis in children are extremely unsatisfactory for evaluation because little attempt has been made to differentiate between the fibrosis following toxic hepatitis and portal cirrhosis. As far as one can gather, most of the reported cases represent the fibrosis following toxic hapatitis.

Inasmuch as the liver is an important storage organ for vitamins, various vitamin deficiencies may result from portal cirrhosis as well as act as the cause. Haig and Patek (40) found that 92 per cent of decompensated cases of portal cirrhosis had vitamin A levels below the lowest normal level. This was accompanied by abnormal dark adaptation. We have already referred to the common evidence of vitamin B deficiency in portal cirrhosis. As another evidence is the increase in pyruvic acid content of the blood, in beri beri (41). In advanced cases, the response to vitamin B therapy may be completely lost. Vitamin C deficiency is not common in portal cirrhosis (1), probably because other organs take up the storage function. Vitamin D insufficiency in portal cirrhosis is manifested by the occasional occurrence of osteoporosis in advanced cases (1). Vitamin K deficiency on the other hand is common in portal cirrhosis, not only because the liver manufactures substances like bile which is necessary for the proper absorption of vitamin K from the intestinal tract, but also because the liver is concerned with the formation of prothrombin which requires vitamin K

for its activation in blood coagulation; and finally, because its function as a storehouse for vitamin K is seriously affected. These factors account in part for the hemorrhagic tendency so common in hepatic disease and particularly in portal cirrhosis.

*Serum proteins and portal cirrhosis.* The finding of a low blood serum albumin in experimental cirrhosis is paralleled in human portal cirrhosis. This was first determined by Gilbert and Chiray (42) and has been repeatedly confirmed (43, 44, 3 and 45). In a large series, Post and Patek (46) found that the serum albumin level possessed a mean average of 2.3 mgm. per cent in patients with ascites, and a mean value of 3.7 per cent in those without ascites. The total serum protein had an average of 6.3 per cent in those with ascites and 7.3 per cent in those without ascites. The globulin fraction was the same in both groups so that the albumen-globulin ratio was reversed. The loss is not due to protein starvation because high protein feeding has no effect on the hypoabuminemia. Post and Patek (47) in a study of 5 patients found that they remained in nitrogen balance on high protein feeding, although the serum albumen levels did not change. The albumen loss is not primarily due to ascites because such a loss occurs even when there is no ascites; however the formation of ascites of any considerable degree aggravates the protein loss. After withdrawal of the ascites, the loss of protein may be profound, since the ascitic fluid contains considerable protein, varying between 0.1 and 1.7 mgm. per cent (44). Most of this protein represents the albumen fraction. The consensus of opinion is that the hypoalbuminemia is due to the impairment of the normal liver function in synthesizing protein. Indeed a lowering of the serum albumen is common in most disorders of the liver accompanied by considerable destruction of the parenchyma. It occurs even in experimentally induced toxic cirrhosis. Moreover, there is strong evidence that the serum albumen is formed in the liver while the globulins may be formed elsewhere (48).

The prognosis becomes increasingly grave as the level of the blood serum albumen decreases, and clinical improvement is associated with a rise. A rise is also associated with a copious diuresis (46).

The low serum albumen is unquestionably the predominant cause for the ascites, and the not infrequent hydrothorax and ankle edema. Ankle edema has in the past been ascribed to the pressure of the ascitic fluid on the vena cava, but ankle edema occurs even in the absence of ascites, and is directly related to the ciritical edema level of serum albumen (3).

The hypertension of the portal circuit undoubtedly contributes to the production of ascites, especially if the pressure within the venous loop of the capillaries is markedly increased, which is apt to occur in the terminal phase. However this increment of fluid is secondary, since the diminution of the blood serum albumen antedates any clinical evidence of hypertension of the portal circulation.

The serum proteins have been examined electrophoretically. Luetcher (49) and Longsworth, Shedlowsky and McInnes (50) found an increase in the $\beta$ and $\gamma$ globulins and a decrease in serum albumen. Gray and Barron (51) found that the abnormality in the electrophoretic pattern depended on the severity of the

disease. The most characteristic abnormality is a large increase in $\gamma$ globulin and a low serum albumen.

*Latent portal cirrhosis.* Inasmuch as the incubation period of portal cirrhosis is one of years, one may presume that there is a dormant period before any marked clinical manifestations arise. This may be termed the compensated phase, and the only clinical evidence may be an enlarged liver. Indeed the number of cases in which a latent cirrhosis is found at autopsy is a considerable one; according to Ratnoff and Patek (4) in their large collected group, 11 per cent. Of 245 portal cirrhoses, McCartney (52) found a latent cirrhosis in 35.5 per cent. He defined latent cirrhoses as those that were not accompanied by jaundice, ascites or esophageal varices, even when hepatic disease had not been diagnosticated clinically. The distribution of the active and latent cases according to decades was identical, but the latent cirrhoses tended to be less advanced than the active group. The livers which showed a more advanced degree of cirrhosis tended to be smaller than those in which the process is less advanced. This was particularly true of those which gave rise to symptoms. An enlargement of the spleen was more frequent in active than in latent cases. Of 167 cases of portal cirrhosis that were observed at post-mortem by Rolleston and McNee (53) 52 per cent were latent.

The question arises whether or not these latent cases would have proceeded inevitably to the terminal phases. The answer hinges upon whether a clinical "cure" of portal cirrhosis is possible even though an anatomical cure is not. This cannot be answered with any assurance. Cases have been reported in which a cirrhosis has remained dormant for many years, but inasmuch as the life cycle of portal cirrhosis is long, one cannot be assured that even such cases might have progressed in time. The problem is further complicated by the fact that portal cirrhosis occurs in the senescent years with its incidental morbidity. Thus it is interesting to note that McCartney (52) reports as the commonest causes of death in latent cirrhosis, heart disease, accident, intestinal carcinoma, pneumonia and cerebral hemorrhage. Even if portal cirrhosis does not kill directly it may be therefore a predisposing cause, since it is well known that such patients are unusually susceptible to infection. Both in latent and active cirrhosis the incidence of fatal pneumonia and other infections is high, approximately 20 per cent (52).

*Relation of estrogens in portal cirrhosis.* Estrogen introduced into the portal system either by organ transplantation or by injection into castrated female animals does not cause estrus (54). In heart, lung, liver perfusion experiments it was found that estrogen was inactivated by the liver (55). Zondek (56) discovered that by mixing liver mash with estrogen that the latter was inactivated. Biskind and Biskind (57) found in vitamin B deficient female rats that there was a markedly diminished activation of estrone in the liver, and recently Singher, Kensler, Taylor, Rhoades and Unna (58) found that in riboflavin and thiamin deficient rats liver slices were unable to inactivate estradiol, while pyridoxin, pantothenic acid, biotin and vitamin A had no effect upon the inactivation. In castrated female rats poisoned with carbon tetrachloride and

alcohol estrogenic substances did not produce activation of the uterus (59). Glass, Edmondson and Soll (60) in all their cases of advanced liver cirrhosis, noted no combined but high free estrogen values in the urine and low or negative androgen values; and they suggested that the gynecomastia and testicular atrophy so frequently observed in advanced male cirrhotic patients were the result of the failure of the cirrhotic liver to inactivate estrogens. Marrione (61) who found testicular atrophy in 57 per cent of 28 cases of Laennec cirrhosis, ascribes the same etiological mechanism. These observations may also account for the frequent impotence in patients with portal cirrhosis.

These observations are of special interest because gynecomastia, testicular atrophy and the smooth skin and feminine distribution of the hair in males with portal cirrhosis have been ascribed in the past as evidences of a constitutional background.

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CHAPTER 14

# GLOMERULONEPHRITIS

Between its beginnings and ends, glomerulonephritis may be converted into many clinical syndromes. Some of these syndromes have received different connotations in the past, with the implication that they represent distinct disease species, whereas, in fact, they are merely transitional states. The reason mutation occurs in one or the other direction is not known, although our knowledge of the pathogenesis of glomerulonephritis is fairly clear. To appreciate the biology of glomerulonephritis, it is essential to observe cases from the beginning to the end. Unfortunately, this opportunity is not always at our command and in hospital practice, especially, one is usually in the position to observe only the middle or terminal phases of the disease. Exceptionally, one may laboriously reconstruct the earlier clinical phases. The following observations are based upon a study of a considerable number of cases from the initial to the terminal stage.

*Etiology.* There is a distinct relation between infection by the streptococcus and glomerulonephritis. The most common focus of invasion is the throat; less commonly, the attack follows scarlet fever. These account for about nine-tenths of glomerulonephritides. In the remainder, are those following streptococcus pneumonia or skin infections. Some cases of "war" nephritis have also been shown to be glomerulonephritides. While the relation of the streptococcus to glomerulonephritis is close, we are by no means clear as to the mechanism whereby this organism causes these lesions; aside from the embolic glomerulonephritides of subacute bacterial endocarditis (a lesion quite different in its morbid anatomy) the streptococcus has never been found in such kidneys. Moreover, these lesions have never been satisfactorily produced experimentally by the streptococcus or any of its known toxins. In all likelihood, the explanation lies in the experimental work of Masugi (1) who produced what appears to be typical anatomical and clinical glomerulonephritis by the injection of kidney antibodies. This suggests strongly that sensitization and the development of resistance to the streptococcus is in some way related to the pathogenesis of human glomerulonephritis. This helps to explain why the glomerulonephritis does not arise at the

height of the infection but only when it is subsiding, but it does not explain why the lesion is often progressive despite the disappearance or removal of the "focus."

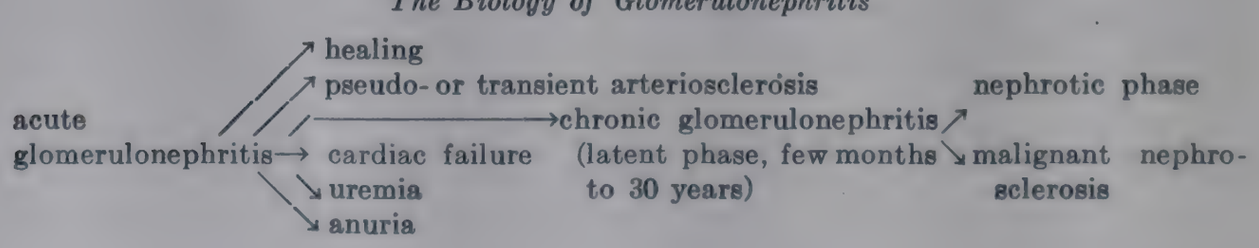
There is reason for believing that glomerulonephritis merely represents the localized expression of a general capillary disease.

*Pathology.* The earliest lesion is represented by a diffuse swelling of the intra- and extra-capillary endothelium of the glomerular tufts, so that the glomerulus appears bloodless and seems to distend the capsule of Bowman. These cells soon proliferate, especially those lining the margins of the capsule, resulting in the formation of crescents. Young fibroblasts appear throughout the parenchyma, particularly in the neighborhood of the glomerulus. Grossly, in this stage, the kidney is large and white. The subsequent changes in the kidney depend upon the growth and senescence of the newly formed connective tissue. Thus we find fibrosis both within and without the capsules of Bowman, with progressive circumferential shrinking of the glomerular tufts to eventual disappearance, so that the glomerulus becomes converted into a mass of newly formed connective tissue. There is also progressive thickening and fibrosis of the intertubular connective tissue, with resulting deformity, obliteration or dilatation (compensatory) of the tubules. In this stage, the surface of the kidney is finely or coarsely granular, the capsule is adherent and the kidney is somewhat shrunken, the degree depending upon the age of the lesion. If the process continues, further maturation of all these elements results in almost complete obliteration of the normal morphology, the contraction becomes extreme, and there results the secondary contracted kidney which may be red due to the congestion resulting from an associated cardiac complication. Coincidentally, changes in the larger blood vessels occur. These have been studied by Fishberg (2) and consist in proliferation of the intima and elastica, in a notable hypertrophy of the muscular coats of the arteries, and, if hypertension is extreme as in the so-called malignant hypertension, in necroses of the vessel wall; in other words, arteriosclerosis is produced, not only within the kidney but in the arteries of the greater circulation. The arteriosclerosis, it may be added, is not the direct result of the inflammatory process but is due to the superimposed hypertension.

In every stage, profound changes in the tubular epithelium occur in the form of fatty and hyaline degeneration or cloudy swelling.

It is important to recognize that the victim may die in any stage of this pathogenesis, even in the earliest. Furthermore, it is impossible to predict the pathologic findings from the clinical data, except in only an approximate fashion. By and large, the longer the duration as disclosed by the history, the more advanced the lesions.

*The Biology of Glomerulonephritis*



*Clinical Evolution of Glomerulonephritis:* 1) *Normal course of acute glomerulonephritis.* The disease occurs in young individuals as a rule and usually two to four weeks after the onset of the infection; the first symptom is proteinuria with hematuria and many coarsely granular and blood casts. Puffiness of the face or extremities occurs early, suggesting generalized capillary disease with increased permeability; the blood pressure rises, rarely to untoward heights. There is usually some azotemia which is rarely marked, and headache. If the diastolic pressure rises to 120 mm. Hg. or higher, hemorrhages or exudates appear in the retina. Occasionally, hypertension of the cerebrospinal circuit arises with marked cephalalgia, disorientation, twitching, convulsions, increased reflexes and occasionally papilledema. This complication, however, is uncommon. I have also seen death occur with complete anuria and marked axotemia, with only a moderate grade of hypertension. Usually, improvement ensues within a few weeks after the onset. The subjective evidences disappear, the azotemia returns to normal, the puffiness and hematuria and hypertension subside. The proteinuria persists the longest, sometimes for weeks or months after all other evidences of nephritis have gone. With the subsidence of the hypertension, the eyegrounds return to normal.

The prognosis cannot be gauged by the severity of the signs or symptoms. I have witnessed severe cases get well and mild cases pass into the chronic phase. As a general rule if the proteinuria persists for three months, the probability is strong that the disease will become chronic. In only one instance, have I seen recovery after a six months persistence of the proteinuria.

Death in the early stages is more likely to occur from left myocardial failure than from uremia. Apparently the myocardium is not adjusted to the sudden onset of hypertension even when the pressure is not excessive and therefore fails if an undue strain, particularly an excessive ingestion of fluid, is placed upon it.

2) *The syndrome of pesudo or transient arteriosclerosis.* Some years ago, I (3) reported eight such cases with one autopsy. Since then I have seen many more, so that it is not uncommon. It is best observed in young individuals in the earlier stages of the nephritis. The radial arteries feel decidedly thickened. As a rule, the diagnosis is made of an "acute nephritis superimposed upon a chronic one." Curiously, as the patient improves and the hypertension subsides, the feel of thickening disappears, but not when the tension returns to normal, but two to four weeks later. This feeling of thickening is therefore not due to the increased intravascular tension alone, but to the disappearance of the hypertrophy of the muscular layers of the vessel wall, a lesion which Fishberg (2) has emphasized is compensatory to the hypertension, comparable in mechanism to the hypertrophy of the left ventricle. As Fischer and Schlayer (4) demonstrated, the sensation of thickening which an arteriosclerotic vessel affords is due more to the hypertrophy of the muscularis than to the changes in the other coats of the vessel. In the case which ended fatally, no arteriosclerosis of the aorta was demonstrable. The remainder recovered completely.

3) *The latent or proteinuric phase of glomerulonephritis terminating in malignant nephrosclerosis.* This is an exceedingly common sequence of acute glomerulonephritis. We refer to patients who have lost every sign and symptom, including

hypertension, and the only remaining evidence of renal disturbance is a persistent proteinuria, usually of moderate grade. These are the patients so frequently encountered in practice who are rejected by insurance companies. It can be easily distinguished from orthostatic albuminuria because in glomerulonephritis there is always morning proteinuria. Unless one has observed such transitions, these cases may be difficult to interpret, especially when hypertension is lacking. We are so accustomed to thinking of hypertension being a part and parcel of clinical glomerulonephritis that it is difficult to believe that this disease may exist without an elevated pressure in some portion of its biological course.

This latent period of glomerulonephritis may last for months or even many years. I published (5) a case of proved glomerulonephritis which began 32 years previously. Unless cut down by intercurrent disease the patient slowly develops signs of renal insufficiency. The kidney loses its power of concentration, azotemia arises, hypertension develops with resulting cardiac manifestations and eye-ground changes, and ultimately, the patient dies with all the evidences of so-called malignant nephrosclerosis. At autopsy, necroses of the vascular wall are nearly always found, undistinguishable from those witnessed in the malignant nephrosclerosis arising from "essential" hypertension.

Some hold that an acute glomerulonephritis may completely heal without a clinical vestige remaining and may relight in later years resulting in the clinical manifestations of hypertensive disease. Such a sequence is particularly plausible when there is a history of scarlet fever or some other streptococcus infection in childhood. In every such instance that I have observed, the kidneys at autopsy revealed the nephrosclerosis associated with essential hypertension and not a glomerulonephritis. In my experience, once an acute glomerulonephritis heals completely, it remains so, and when it becomes chronic there is always a clinical continuity from the acute stage. And here a distinction must be made between clinical and anatomical healing. Clinical healing does not necessarily imply a complete anatomical *restitutio ad integram*. Being a productive inflammation, it is difficult to conceive that such a kidney can be restored to its previous integrity, but the anatomical appearance of such an organ, when clinical healing has occurred, is still unknown. It is difficult to find such kidneys because a number of checks are necessary. There must be proof 1) that a true glomerulonephritis occurred in the past 2) that clinical healing occurred and 3) the patient died without any evidence of renal involvement.

4) *The nephrotic phase of glomerulonephritis.* This evolution of acute glomerulonephritis will be discussed more fully in the chapter on "nephrosis." All we need say at present is that it occurs only when sufficient protein is lost by way of the urine to provoke a hypoproteinemia.

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CHAPTER 15

# OBESITY

"Leave gormandizing: know the grave doth gape
For Thee thrice wider than for other men"
Shakespeare, Henry VIII.

In this chapter, we shall not enter into the much debated causes of obesity because the ultimate effects are to a large extent independent of the cause.

*Life expectancy in obesity.* Dublin and Lotka (1) analyzed the duration of life in close to 200,000 men aged 21 and over according to weight. The following tables tell the story.

From these tables it is obvious that obesity shortens life proportionately to weight and age. The figures also imply that the longer the duration of the obesity, the worse is the life outlook.

TABLE I

*Influence of weight in mortality: deaths per 100,000 men accepted for insurance*

| WEIGHT | DEATH |
|---|---|
| Standard | 844 |
| Underweight total | 848 |
| Overweight total | 1111 |
| Overweight 5–14% | 1027 |
| Overweight 15–24% | 1215 |
| Overweight 25% | 1472 |

TABLE II

*Influence of weight in mortality, as modified by age*

Deaths per 100,000

| WEIGHT | AGE (YEARS) | |
|---|---|---|
| | Under 45 | Over 45 |
| Standard | 463 | 1308 |
| Underweight, total | 498 | 1274 |
| Overweight | 527 | 1824 |

TABLE III

*Influence of overweight on mortality in persons 45–50*

| POUNDS OVERWEIGHT | INCREASE IN DEATH RATE AVERAGE PER CENT |
|---|---|
| 10 | 8 |
| 20 | 18 |
| 30 | 28 |
| 40 | 45 |
| 50 | 56 |
| 60 | 67 |
| 70 | 81 |
| 80 | 116 |

*Relation of obesity to diabetes mellitus.* The common association of obesity with diabetes is a well confirmed clinical observation. Joslin and his associates (2) report that among 1000 successive diabetics the maximum weight of only 8 per cent was below the standard, 15 per cent were in the normal zone and 77 per cent were above it. Between the ages of 51 and 60 there were only two diabetics in 252 whose maximum weights were below the normal zone prior to the onset of the disease. Among 2000 of their patients none occurred who was more than 30 per cent underweight. In all groups, there was a greater frequency in women. Moreover, actuarial statistics (Joslin, Dublin and Marks (3)) reveal that diabetes develops more frequently in obese individuals than in those of normal weight, and that the increase is proportionate to the weight.. The mortality statistics parallel the impairment statistics. Inasmuch as diabetes mellitus is insidious in onset one would expect that a prediabetic state would be found in some instances of obesity and testimony is abundant that it does occur frequently as determined by a glucose tolerance test. Berler and Fitz (4) in 32 cases of obesity found that a considerable number had typical diabetic curves. John (5) found a diabetic curve in 65 per cent with a high renal threshold (above 180 mgm. per 100 cc.), in 46 per cent, Embleton (6) found high glucose tolerance curves in 73 per cent of male obese patients and in 35 per cent females but up to the age of 35, high tolerance curves were noted in only 27 per cent of the males and in 23 per cent of the females. He did not find that the per cent of high glucose tolerance curves increases pari passu with the increase in weight. Short and Johnson (7) report that there was an unmistakable correlation between the degree of the overweight and the incidence of impaired glucose tolerance, irrespective of age.

The large incidence of high tolerance curves in obesity is only of significance when the time factor is taken into consideration, for such curves obviously do not spring up over night. Age alone has an effect on the incidence of impaired tolerance [Bertram (8), Marshall (9), Spence (10)]. Spence found a progressively higher glucose tolerance test from the third year of age on. John (11) in comparing the glucose tolerance curve of children and adults found that 82 per cent of children had normal curves, and 62 per cent adults. Short and Johnson found that age has a slight effect on the incidence of impaired tolerance; this was most noticeable from the 7th decade onward.

Under these circumstances the effect of obesity would have an added significance not only in relation to age, but also in regard to the duration of the obesity. Ogilvie's (12) study is particularly impressive in this regard. When sugar tolerance tests were plotted according to the duration of the obesity, he found that during the first 5 years of obesity, one-third of his patients showed an increased tolerance for sugar. After this period, the tolerance lies within normal limits up to the eleventh year of the obesity. After this year, diminished tolerance makes its appearance and after 18 years of obesity, every case shows a lowered tolerance and diabetes appears. Short and Johnson also think it probable that the duration of overweight determines the incidence of impaired tolerance. They hold that the two factors, age plus the degree of overweight accentuate the incidence of diminished sugar tolerance. In accordance with this evolution, Ogilvie (13) found hypertrophy of the islands of Langerhans in 13 of 19 subjects with obesity, most of them 49 years of age and upward, which he believes is compensatory for the excessive carbohydrate intake that so frequently initiates and continues the obesity. Inasmuch as no other study is available in reference to the hypertrophy of the islands of Langerhans in the early or prediabetic phase of obesity, Ogilvie's observations await confirmation but in this connection the finding of hypertrophied islands in babies of diabetic mothers is suggestive, [Gray and Feemster (14)], [Gordon (15) 4 of 4 infants], [Warren (16) 6 of 9 infants], [Helwig (17) 4 of 9 infants], [Potter, Seckel and Stryker (18) 2 of 4 infants], especially as most of these babies were overweight. The percentage of incidence is too high to be a matter of mere chance. That the hypertrophy is not specific is proven by their occasional presence in infants of non-diabetic mothers. Both Helwig and Potter and his associates found no correlation between the blood sugar and the morbid changes. The hypertrophy of the islands in association with the usual excessive weight of the infants suggest, as Ogilvie and Helwig assert, that the mechanism is a compensatory one, to meet the growth stimulus engendered by the hyperglycemia of the mother.

Additionally corroborative in this respect is the occasional occurrence of symptoms of hyperinsulinism in cases of obesity. I have recently seen two cases. Harris (19) probably refers to it under the term "dysinsulinism" and Conn (20) as "essential hyperinsulinism." Conn describes an illustrative case in a young obese girl whose fasting blood sugar was normal. This in his experience, differentiates it from hyperinsulinism of organic origin, wherein the fasting blood sugar falls to hypoglycemic levels by provocative methods. Essential hyperinsulinism according to Conn's view represents an exaggeration of the normal insulinogenic effect in healthy individuals who partake of a high carbohydrate diet. This observation is substantiated by the work of Horst, Ridout and Best (21) who found that animals deprived of food for 7 days have much less insulin in the pancreas than well fed animals.[1] At all events, a vicious circle is established and the sequence of events may be described as follows. As a result of

[1] Soskin (22) holds that the hypoglycemia curve following excessive carbohydrate ingesction is not due to insulinogenesis but to the fact that the liver fails to pour glycogen into the blood under the influence of a high carbohydrate intake. His views while provocative have not been widely accepted.

a high calory diet due to whatever cause, there is a compensatory overstimulation of the insular tissue. This induces a further craving of carbohydrates to satisfy the hunger, which again adds to the weight and so on. Whether eventually exhaustion of the insular apparatus results and diabetes develops in all instances will not be known until patients with essential hyperinsulinism have been followed over a long period of years.

Particularly suggestive in this connection is the experimental production of diabetes by anterior pituitary extract. Anselmino, Herold and Hoffman (23) found that the administration of anterior pituitary extract to normal rats resulted in substantial hyperplasia in the islands of Langerhans. They ascribe this increase to the action of a "pancreatotropic hormone" in the pituitary gland. Simultaneously they found an increase in the amount of insulin in the blood. Richardson and Young (24) found in rats by quantitative determination that the amount of islet tissue in animals that received daily injections of anterior pituitary extract for some weeks was double that of control animals. Marks and Young (25) found that the insulin content of the pancreas of the pituitary treated rat may be twice that of control animals suggesting that the extra islet tissue formed as the result of the hypophyseal stimulus is functionally active. On the other hand, in animals made permanently diabetic by anterior pituitary extract, the islands showed changes varying between depletion of the cytoplasmic granules of the beta cells (hydropic degeneration) to complete replacement by hyaline substance. This is the theory suggested by Falta (26) and it seems attractive because it accords with such available data that strongly indicate such a biological evolution. Moreover, there are other analogies in clinical medicine where hyperactivity passes into hypofunction, for instance, the occasional development of hypothyroidism after a long continued hyperthyroidism. But the problem of the relationship of obesity to diabetes will never be solved until systemtic morphological and functional studies are conducted throughout the entire life cycle of the disease.

Obviously, in this discussion we must remember that the glucose tolerance test does not exclusively represent the function of the insular apparatus of the pancreas. Furthermore, the glucose tolerance test is modified by the previous diet of the patient (Conn), by the alkaline reserve and by other associated conditions. In any event, the glucose tolerance test is the best means at our command to determine a prediabetic state. One must also remember that when a prolonged and marked hypertension complicates obesity, the threshold for glucose rises sometimes to a considerable degree, as the direct consequence of the hypertension. Most hypertensives may therefore be regarded as potential diabetics. This factor modifies the incidence of diabetes in obesity to a considerable extent.

Recently, Newburgh and Conn (27) reported a series of overweight individuals, usually over 30 years of age, with spontaneous glycosuria and a high tolerance curve who were made sugar free by merely inducing a reduction in weight. They do not become hyperglycemic and the glucose tolerance curve becomes normal on a maintenance diet of 300 gms. carbohydrate provided they do not gain weight. Ninety per cent of such patients follow this rule, the other ten per cent do not.

A recurrence of the obesity reproduces the original picture. They suggest that this syndrome is due to the excessive accumulation of fat in the liver with a resulting impairment in the ability to accumulate glycogen at the normal rate. It is highly doubtful whether this syndrome is a distinct entity, nor can one say that these patients are "cured" because their glucose tolerance curve is normal and they have no glycosuria. The probability is strong that these patients represent a stage in the evolution of a true diabetes, and a long follow-up is highly essential to determine the ultimate fate of such patients.

It is very apparent that the diabetes that follows obesity is a matter of slow development, conditioned by many factors, amongst others, heredity, and it is difficult to gauge, as in so many of the hyperkinetic diseases (28), when the transition from health to disease has occurred.

*The relation of obesity to hypertension.* Even in individuals within the range of normal weight, the blood pressure is in general proportionate to weight. Thus Alvarez and Stanley (29) found in prisoners that weight tends to increase the pressure after the age of 35. Even in normal children, Michael (30) found a correlation between systolic pressure and weight and height. In soldiers, Huber (31) found that hypertension is closely correlated with weight above the standard. Dublin, Fisk and Kopf (32) found a higher percentage of hypertension (20 mm. Hg. or more above a normal blood pressure for age) in overweight persons, than in those of normal weight. This correlation was especially marked as age advanced. The following table is based on large actuarial statistics (33).

TABLE IV

| PER CENT | AVERAGE BLOOD PRESSURE MM. Hg | |
|---|---|---|
| | Systolic | Diastolic |
| underweight (−)<br>overweight (+) | | |
| −35 to −26 | 117.7 | 77.0 |
| −25 to −16 | 120.6 | 79.2 |
| −15 to −6 | 122.4 | 80.8 |
| −5 to +5 | 124.1 | 82.1 |
| +6 to +15 | 126.1 | 83.7 |
| +16 to +25 | 127.4 | 84.7 |
| +26 to +50 | 127.8 | 84.8 |

Gager (34) found that 28.3 per cent of obese patients of all ages had hypertension against 16.4 per cent of the non-obese. Master and Oppenheimer (35) in a study of obesity found that 67 per cent showed a hypertension of 150 mm. Hg. or over and that the height of blood pressure was correlated with the weight and especially with age. Symonds (36) conclusions are identical. Terry (37) found 58 per cent of his obese patients hypertensive, averaging 176 to 96 mm. Hg. After reduction of the weight, the average blood pressure was 170 systolic and 95 diastolic; it is evident therefore that the diastolic pressure is more resistant to the reduction than the systolic. Short and Johnson (38) in a study of 2858

applicants for insurance found that overweight exerted a positive influence in causing an increased incidence of hypertension, and the difference in average blood pressure was greatest in the sixth decade. He found the incidence less than the other observers. The hypertensive effect of gaining weight is well illustrated in Cushing's syndrome.

It is evident therefore, that weight plus age is a conditioning influence upon the development of hypertension. As corroboration, one may cite the reduction in blood pressure that is usually attendant upon a loss of weight, as Terry observed. This is especially noticeable in the early or labile phase of hypertension. Indeed, I have seen a moderate hypertension return to normal pressure levels and remain so for many years, and the more pronounced the weight and the earlier it is treated, the greater the reduction in blood pressure that may be expected. Again the diastolic pressure, as Terry observed, is less influenced than the systolic. Even in individuals of normal weight the reduction of a few pounds sometimes influences the pressure considerably. One cannot divorce temperament in the development of hypertension in the overweight. As I tried to show in Chapter 2 (Biology of hypertension of the greater circulation) hypertension is more apt to occur in temperaments that may be described succinctly as the antithesis of the child in mental make up. They usually overeat and do not play or take much exercise, factors which contribute toward overweight. This type of individual, in my experience, is more subject to the development and the hastening of the tempo of hypertension than stout individuals who have the conventionally recognized happy, playful and childlike temperament.

The mechanism whereby overweight raises the blood pressure is not entirely clear. I suggest that it is a compensatory effect to meet the extra burden placed upon the heart which does not always keep pace in size and weight with the growth of the body [Hirsch (39), Smith and Willius (40)]. This might explain the reduction in blood pressure after losses of weight, and the notorious tendency to a low blood pressure in thin individuals. This mechanism may also serve as the explanation for the steady rise in blood pressure, both systolic and diastolic, (although both are within the normal range) in normal pregnancy. [For literature see Jensen (41).]

The observations of Wood and Cash (42) are also suggestive. In dogs made hypertensive, the systolic pressure rose with gains in weight and fell with weight loss. The diastolic pressure varied little.

It is important to appreciate that primarily obesity causes a hypertension of the greater circulation only. This is also true of the experimental hypertension produced by Goldblatt [Katz (43)]. Obesity produces hypertension of the pulmonary circuit only after left sided failure has been initiated. For the final phase in hypertension of the greater circulation, see Chapter 2.

*The relation of obesity to cardiac disorders.* Obesity may affect the heart function in other ways than through the intermediacy of hypertension. The "fatty" heart or the "beer drinkers" heart no longer possesses the significance attached to it by the older generation of clinicians. This is largely due to the introduction of instruments of precision to measure cardiac function. Nevertheless, "fatty

infiltration of the heart"[2] to a limited degree affects cardiac function, sometimes profoundly.

Müller (44) found that under normal circumstances, the size of the heart increased proportionately to the weight, according to the following table.

TABLE V

| WEIGHT IN KGM. | RIGHT VENTRICLE | LEFT VENTRICLE | SEPTUM |
|---|---|---|---|
| | | Men | |
| 30–40 | 40.4 | 75.7 | 54.7 |
| 40–50 | 47.1 | 84.5 | 63.2 |
| 50–60 | 55.6 | 103.4 | 73.9 |
| 60–70 | 61.6 | 120.0 | 84.1 |
| 70–80 | 66.1 | 131.3 | 90.5 |
| | | Women | |
| 30–40 | 28.9 | 52.9 | 40.0 |
| 40–50 | 37.7 | 66.8 | 50.4 |
| 50–60 | 41.9 | 79.9 | 57.5 |
| 60–70 | 49.7 | 92.7 | 65.9 |
| 70–80 | 56.5 | 97.4 | 75.7 |

Hirsch (39) many years ago, found that in obesity the heart does not increase in size commensurate with the growth of the body, which he believed accounted for the premature heart failure. Smith and Willius (40) in a study of heart failure in obesity arrived at the same conclusion. In a fourth of their cases of obesity without primary disease of the heart, the actual weight was less than the calculated weight. They found that many factors were involved in the production of failure in obesity, the most important being, first, the fatty infiltration of heart which often penetrates as far as the endocardium and which, as a rule, involves the right heart to a proportionately greater degree than the left; and second, the increased amount of work to be performed to satisfy the excess of tissue to be nourished and the increased metabolism of the patient. Smith and Willius report 9 cases, most of them dying in heart failure. in which primary evidence of disease was lacking. These patients had no hypertension or any previous hypertension, and all were very obese. These observations of Smith and Willius prove that hearts in the obese may occasionally fail in the absence of pathological changes.

As the result of the high diaphragm, the heart is displaced upward and acquires a more horizontal position with a rotation of the electrical axis. Fishberg (45) believes it plausible that this displacement contributes to the handicap.

Wiggers (46) suggests another factor that no doubt influences the work of the heart in obesity. The heavy deposit of subcutaneous fat acts as a poor con-

[2] Fatty infiltration is not synonymous with fatty degeneration. The latter lesion is an intracellular lesion as opposed to an intermuscular deposition of adipose tissue, and is usually of toxic origin.

ductor of heat which decreases the capacity for heat elimination. To compensate, fat people perspire profusely. This leads to excessive ingestion of fluid resulting in increased blood volume, increased venous return and increased work of the heart. This explanation obviously also necessitates a time factor.

The heart in obesity may also be affected indirectly through the effect upon the respiratory organs. Prodger and Dennig (47) and Bowen (48) found the vital capacity diminished; the latter in some instances, found it 20 per cent below normal. Furthermore, Prodger and Dennig, found the respiratory minute volume increased during exercise, the respiratory rate was increased in the sitting position and an increased oxygen consumption during exercise. Directly, these factors are responsible for the dyspnoea. They also confirmed Lichtwitz's (49) finding of an increase in lactic acid in the blood, suggesting that even in the early stages of obesity, there is already beginning circulatory insufficiency.

Clinically, it is well known that obesity aggravates the prognosis of any cardiac disorders, no matter of what origin.

Summarizing, there are a host of factors, given time, that may cause grave myocardial insufficiency in obesity, independent of hypertension or coronary disease.

*Relation of obesity to cholelithiasis.* That obesity predisposes to cholelithiasis is well known and the stones are usually of the cholesterol type. The reasons therefore are concerned in the problem of the pathogenesis of gall stones in general. There is probably some disturbance in the metabolism of cholesterol, although the blood cholesterol is usually within the range of normal in obesity. [Bruch (50), Bruger and Poindexter (51)]. Nor is the content influenced by a low calory diet. In all likelihood, the stagnation of the biliary contents by lack of exercise, which as Winkelstein (52) has shown tends to propel the bile from the gall bladder, is a contributing factor.

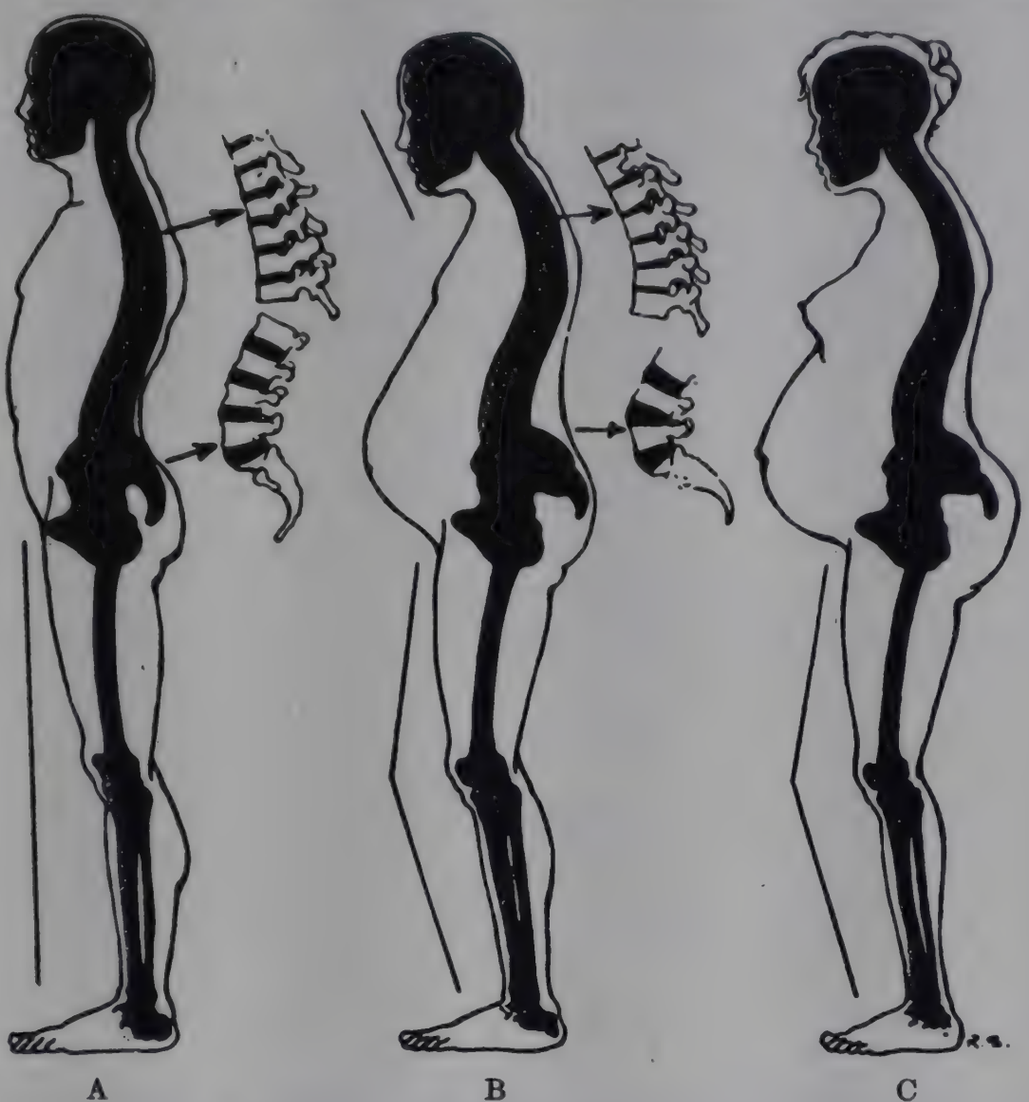
*The effect of obesity upon the skeleton.* That the increased weight must handicap the mechanics of the skeletal structure is obvious, not only through the effect of the sheer weight itself but through its distributions. The center of gravity is changed, and as a consequence, the lumbar curve of the vertebra first becomes lordotic; this is followed by a compensatory thoracic kyphosis and eventually a cervical lordosis producing a forward position of the head. These changes Kerr and Lagen (53) call the "postural syndrome" and is well represented in figure 1. Kerr and Lagen explain the emphysema that so often accompanies obesity as compensatory to thoracic kyphosis and the consequent flaring of the ribs.

There are a number of other consequences of an orthopedic variety.

The frequency of flat feet in obese patients is familiar.

One of the commonest disturbances is a bilateral arthritis limited to both knees and sometimes the ankles. This is particularly common in stout elderly women. That this form of arthritis is due to weight bearing is proven by its alleviation when a considerable loss in weight is attained. In the early stages, before morbid anatomical changes in the knees have taken place, such an arthritis is even completely curable.

Some years ago, I (54) called attention to a fairly common inflammation of the sartorius bursa that sometimes follows a long continued obesity, especially in women. It is always bilateral and characterized by tenderness over the inner aspect of the tibial condyle, exactly at the site of the conjoined tendon while motion at the knee joint is perfectly free and painless. The history is rather




**Types of posture showing effects on spine**

A. Posture, spinal curves and intervertebral discs normal.
B. Relaxed posture with accentuated spinal curves resulting from a pendulous abdomen.
C. Postular changes late in pregnancy, similar to those in B, but which never persist long enough to affect the intervertebral discs.

**FIG. 1**

**From Annals of Internal Medicine, 10, 569, 1936, Kerr and Lagen**

characteristic; the pain only arises when going up or down steps, never when walking on level ground.

*Effect of obesity upon the gonads.*[3] Obesity in women frequently is preceded or accompanied by amenorrhea. The basal metabolism of these patients usually is normal. The uterus shows involution and flabby musculature. Hormonal studies of the blood and urine are too variable to be conclu-

[3] For this section I am indebted to my friend and colleague, Robert T. Frank, M.D.

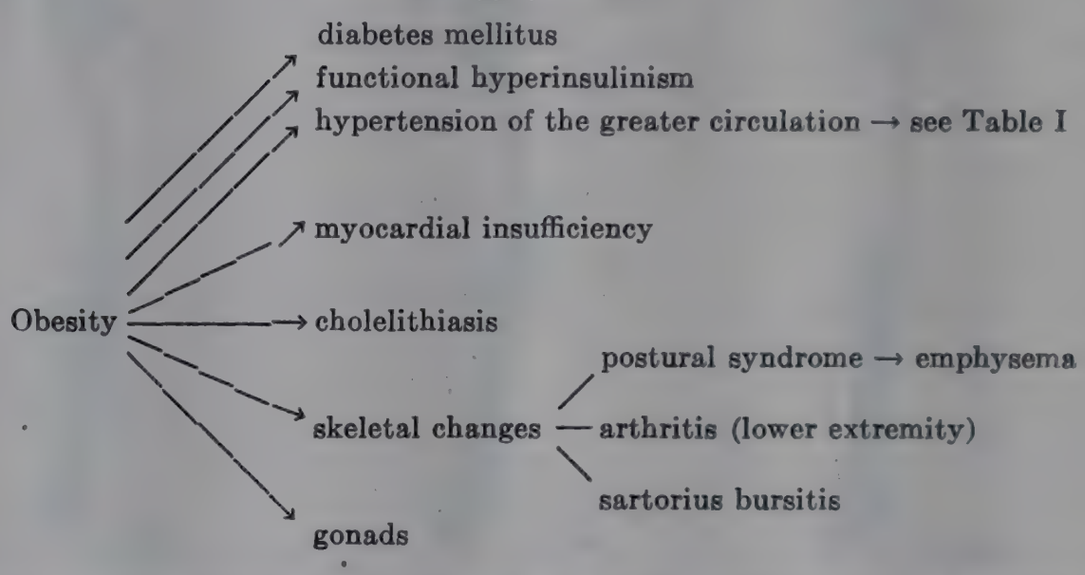
sive. The same applies to uterine biopsies and vaginal smears. The condition is regarded as functional hypo-ovarianism, but this concept is loosely drawn and not based upon convincing anatomical or other evidence.

Reduction in weight by slow continuous diet commonly leads to reestablishment of menstruation after the weight is reduced. Recurrence of the amenorrhea commonly follows regaining of weight. On the other hand, it should be remembered that occasionally very fat patients menstruate normally or suffer from menorrhagia. Amenorrhea almost invariably is accompanied by sterility.

The simultaneous development of hirsutism and obesity indicates a more persistent type. Gradual and smooth transition to the typical adrenocortical syndrome with moon face, pink striae and osteoporosis has been observed. Many of the intermediate groups show neither chemical nor x-ray changes sufficient to warrant an exact diagnosis. Occasionally pituitary disease simulates the less grave affections (erosion of the sella, ocular symptoms, hypoglycemia).

TABLE VI

*The Biology of Obesity*




In the male, obesity rarely produces clear cut gonadal symptoms. Diminution in libido may be complained of but no data as to change in sperm count are available.

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CHAPTER 16

# PEPTIC ULCER

The elucidation of the biology of peptic ulcer is promptly confronted with the hazard that, despite its inordinate frequency, the initial phase is not known. The difficulty arises from the circumstance that the stomach has hitherto been an inaccessible organ. Thus far the one positive clinical criterion of a peptic ulcer is the roentgen ray examination, which unfortunately is diagnostic only after the ulcer has fully matured. A patient either has a peptic ulcer or he has not; the intervening phase has been a matter of wide controversy. Moreover, the result of the roentgen ray examination is often misleading, since an ulcer may be found at operation or autopsy despite a radiographic report of normalcy; this applies even when the ulcer is not situated in an area where its demonstration by roentgen ray examination is notoriously difficult. It is altogether likely that pathologists have seen the earliest change, perhaps in the form of an erosion or a circumscribed granulomatous change in the mucosa, but positive evidence that this lesion represents the larval form of peptic ulcer is still lacking. Serial gastroscopy offers the hope that this consummation will some day be attained.

*Etiology.* In recent years, the view is steadily gaining ground that peptic ulcer is a psychosomatic disease. This view is based on the following observations:

1. There is a characteristic personality or constitution. Ulcer victims are intolerant, all or nothing, mentally inelastic individuals, with strong aggressive, masochistic and sadistic tendencies. They harbor grudges and do not overcome emotional strain rapidly. They are haters and fighters. From the psychoanalytic viewpoint, Alexander (1) finds that ulcer patients suppress the longing for the maintenance or revival of the infantile relation of the child to the mother, because this longing is incompatible with the dominant ambitions of the conscious personality to grow up; to be independent, masculine and active. The suppression remains as a permanent tension. Draper (2) has described various anthropomorphic characteristics of the patient with peptic ulcer, the so-called "lean hungry Cassius" type of individual; the expression is hard and tense, the eyes deep and sullen, the lines of the face are sharply drawn, the mouth is firm, the jaws sharply angled and the masseter muscles are prominent. The patients are usually cyanotic and display tendencies toward erythremia. To what extent these physical characters are phenotypic or genotypic, it is difficult to estimate. Many of the physical characters may be interpreted as results and not as fore-

ordained structures, so that this constitution is probably largely conditioned by factors that began after birth. In this respect, we agree with Alexander. In any event, these physical characters are absent in a considerable proportion of patients with peptic ulcer. The psychogenic characters in my experience, never are.

2. Preceding the onset of symptoms, there can nearly always be elicited the story of an emotional conflict, economic distress, the illness or death of a dear relative, the development of a powerful hate, a resentment against an adjustment to a new way of living. The latter milieu accounts unquestionably for the appalling incidence of peptic ulcer in World War II (3, 4). That the psychological insult activates an ulcer there is little question, if one may judge by the sequence of clinical events. The probability is strong by the same token that a prolonged psychological insult is an important conditioning factor in actually creating an ulcer One cannot account for the sudden onset of the typical symptoms of distress, or for a hemorrhage in one who had previously been perfectly well and had been suddenly thrust into a difficult environment. This set of circumstances has arisen time and again in this war. *Per contra*, a remission following transfer of the patient to a more secure environment, for instance a holiday, is a constant and impressive clinical observation. One may pertinently ask why peptic ulcer is not even more ubiquitous than it is in view of the psychic strain to which most of us are subject. The answer lies first, that the background or constitution is missing; and second, that it is not the psychic strain but the manner in which one meets it that is the determining factor. As White, Cobb and Jones (5) put it "It is not the objective fact of impact which is important, but the way in which it is experienced". In this interpretation a peptic ulcer is the result of the impact of a particular variety of psychic reaction upon a constitution compounded of particular psychological components. When one or the other is lacking an ulcer will not develop. The situation is quite comparable to that which obtains in pernicious anemia; the constitution in peptic ulcer may be compared to the intrinsic factor; the psychogenic insult to the extrinsic. To describe patients with peptic ulcer as "nervous and tense" is totally inadequate, and to ascribe the activating factor to "worry" is equally faulty.

3. Peptic ulcer is extremely rare in children, before the emotive and affective mental attributes develop.

4. There is testimony that peptic ulcer is rare in primitive peoples who live under little emotional conflict (6). For instance, peptic ulcer is rare among the Negroes in Africa, whereas in our northern Negroes it is, in our experience, almost as common as in whites. One must conclude that this is due to conflicts engendered by industrialization and competition.

It appears that peptic ulcer, like all the hyperkinetic diseases (7) is essentially a disease of civilization.

The problem now arises as to how these psychological influences are transmuted into peptic ulcer. Inasmuch as we cannot observe transitions in the human being, the answer must come through the experimental production of an ulcer.

*Experimental production of peptic ulcer.* Numerous attempts have been made to reproduce peptic ulcer in animals, but most have been unsuccessful except by methods that are entirely unphysiological for human beings. Moreover, such ulcers heal rapidly, do not arise in the pathway, and altogether do not resemble those in man. The most convincing results have been obtained by Mann and Williamson (8). Grossly and histologically these ulcers were identical to the human variety, in their chronicity, their morphology, both macroscopic and microscopic, and their characteristic predilection to the pathway. These ulcers were created in two ways. (a) By eliminating the duodenum and sewing the jejunum to the pylorus, and when modifications were added whereby the acid was neutralized, buffered or diluted, the incidence of peptic ulcer was 95 per cent. (b) By repeated administration of hydrochloric acid to normal dogs by continuous drip for eight hours daily, Mann and Bollman (9) created an ulcer in about 4 weeks. Daily repetitions of excess acidity depresses the neutralizing ability. Such ulcers heal in a few days after the acid is discontinued. In the type of ulcer obtained by elimination of the duodenum and its contents, an ulcer appears rapidly, in hours or less than a day. The morphology of the primary lesion represents the prototype of that which we predict will eventually be found in the human stomach. "Macroscopically, they appeared as saucer-like depressions in the mucosa about 2 cm. distal to the pylorus. In their incipience, there is always a ring of mucosa between the ulcer and the pylorus. In the earliest stages, there is a small area covered with a homogeneous gray membrane. When the membrane is sponged off, a slight depression is uncovered where the surface of the mucosa had disappeared and which bled profusely. After the mucosa is eroded, the process may proceed quickly until the wall is perforated. Microscopically, the gray membrane is composed of mucosal cell debris. In the earliest stages the injury involves only the tips of the tubules. Hemorrhages then occur between the tubules underneath the gray covering. As more of the mucosa is injured leucocytic infiltration occurs, the ulcer penetrates beneath the muscularis mucosae and the ulcer assumes the chronic type" (9). These experiments have been confirmed by Gotschlich (10) and Dragstedt (11). These experimental results prove, if nothing more, that the acid factor is vital in the production of peptic ulcer, a fact that has been clinically surmised for decades.

*The acid factor in peptic ulcer.* Aside from Mann and Bollman's observations, the proofs that the acid factor is a fundamental conditioning factor are the following:

1. Hydrochloric acid in excessive quantity is almost an omnipresent accompaniment of ulcer. The rare reports of achlorhydria with peptic ulcer date mostly from the period before fractional test meals and the histamine test reduced the incidence of achlorhydria appreciably and must therefore be viewed with scepticism (12).

2. Recurrence of either peptic ulcer or a gastro-jejunal ulcer following operation does not result, if complete achlorhydria is attained; this has been our experience at the Mount Sinai Hospital.

3. In the rare cases of ulceration of Meckel's diverticulum, aberrant mucosa is nearly always present, and the ulcer is found in the intestinal and not in the gastric mucosa (13, 14, 15). Indeed Matthews and Dragstedt by an ingenious operation whereby the gastric juice is diverted into the jejunum or ileum have reproduced the counterpart of a Meckel's diverticulum with aberrant gastric mucosa, and have obtained an ulcer of the jejunum in 85 per cent and in the ileum in 100 per cent of the experiments. In passing it is interesting to note that in 18 collected cases of peptic ulcer of a Meckel's diverticulum collected by Lindau and Wolff (15), all but 2 occurred in persons below the age of 15 years.

4. In over 800 cases of pernicious anemia, peptic ulcer was not found in a single instance.

5. With the Palmer test (16) in which a quantity of dilute hydrochloric acid is swallowed in suspected cases, the onset of pain is usually indicative that an ulcer is present. In most such instances, the roentgenogram shows definite changes (17).

Recently, Walpole, Varco, Code and Wangensteen (18) by repeated single daily doses of histamine (in beeswax) in cats and dogs produced erosions and all stages of ulceration including acute perforation. "These findings suggest the importance of a gradual liberation of histamine in maintaining a constant and fairly uniform stimulation of acid." Their findings are particularly significant as an explanation of the "curling ulcer" that occasionally follows extensive turns. Necholes and Olsen (19) found experimentally that after extensive burns there is a rapid and sustained increase in gastric secretion amounting to several hundred per cent.

There is every reason to believe that hypersecretion precedes the initiation of human peptic ulcer, although there is no doubt that the ulcer may continue the hypersecretion. After the ulcer has healed, hypersecretion may persist, for a time at least (Crohn, 20). There is no doubt that emotion may produce a temporary hyperchlorhydria (21, 22). Wolf and Wolff (22) demonstrated this beautifully in their laboratory assistant Tom, the victim of a large gastric fistula surgically produced after a complete closure of the esophagus which resulted after drinking hot chowder as a child. Their experiments are particularly pertinent because they illustrate the effect upon the stomach of different varieties of emotion. After an alarm reaction following fear, or after depression the mucous membrane blanched and acid secretion diminished. Following resentment or anxiety, on the other hand, the gastric mucosa was engorged and redder than normal and the gastric secretion in terms of volume and acidity was 3 times that of normal. There was also an increase in the contractions of the organ. The appearance of the mucosa was that usually reported by gastroscopists as "chronic gastritis." Furthermore, when the emotional situation was profound and prolonged, there was a corresponding increase in vascularity, secretion and mobility. These observations were confirmed by Gordon and Chernaya (23) on a patient, the victim of similar circumstances.

A highly significant observation was made by Hoelzel (24) who made daily

observations upon his gastric acidity for years. While he was passing through a period of fear owing to the anticipation of being shot, his acidity rose to appreciable heights. When he left the city so that the occasion for fear ceased, his acidity returned to normal.

Silberman (25) found that sham feeding through an esophagostomy opening in the neck caused a powerful stimulation of the peptic glands with large amounts of fluid acid and peptic titre, and in some animals a peptic ulcer formed. These observations have been confirmed by Buchner (26) and Puhl (27), although in Dragstedt's (11) hands, such an operation was without effect. The evidence is strong that a sustained hypersecretion constitutes one of the intermediary mechanisms between disturbances in the psyche and the formation of an ulcer.

In this interpretation, peptic ulcer may be regarded as a hyperkinetic disease, which means that a large part of the mechanism whereby it is created is the result of a protracted exaggeration of one of the normal bodily functions.[1]

There is little doubt that this exaggeration of normal function is mediated through the autonomic nervous system. Pavlov showed definitely that the vagus nerves are the pathways for the stimuli that created the psychic phase of secretion. There is a decrease in secretion after experimental vagotomy. Indeed, some surgeons practice this method in preparing gastric operations for peptic ulcer.

Many observers have accepted, uncritically we believe, the hemorrhagic erosion as the initial phase of peptic ulcer, because it is so frequently associated with peptic ulcer. These erosions are called acute peptic ulcer or Dieulefoy's ulcer. Some years ago we (28) reported a number of gastroduodenal erosions, in patients who had no pain and in whom the only symptom was hematemesis. We pointed out that these erosions differed from peptic ulcer in a number of ways, aside from the absence of pain. 1. These patients did not reveal the characteristic psyche of peptic ulcer. 2. The erosions are not limited to the pathway. 3. The erosions are frequently unsuspected findings at autopsy, unattended by clinical phenomena and frequently associated with other profound disorders such as shock and sepsis. 4. Such erosions can be experimentally created though with difficulty, by multiple ligation or embolization of the gastric vessels. Such erosions heal within a short time and never give rise to the callous peptic ulcer. As Mann and Bollman state bluntly "If the mucosal lesion in man which precedes the development of the characteristic peptic ulcer begins as a hemorrhage into the mucosa, it appears that many of the results of our investigation would have little if any clinical bearing" (vide supra).

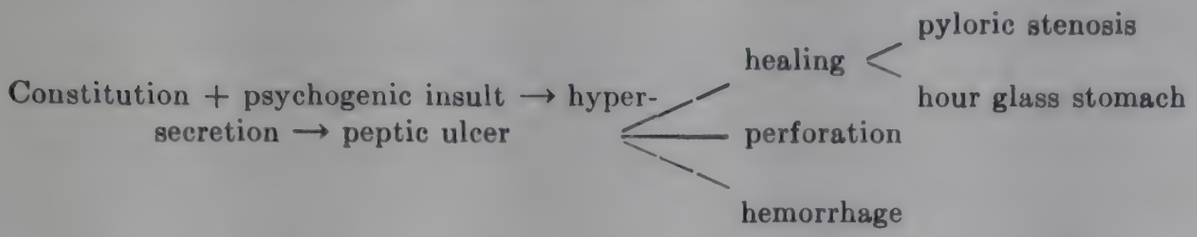
The claim that a "chronic gastritis" is the "cause" of peptic ulcer has contributed nothing to the etiology, because the "cause" of the "gastritis" is still obscure. Even assuming that a "chronic gastritis" is not secondary to the ulcer and that it does not represent a normal senescent change, it does not accord with

[1] It is well to be reminded that in peptic ulcer the titre of the acid never quite attains that of the normal secretion (29). It is the increase in quantity and not the degree of acidity that is the characteristic manifestation of peptic ulcer.

the psychological background of peptic ulcer, its distinctive localization to the pathway, the incidence of the disease in respect to sex and age, and its comparative absence in primitive races, animals and children.

After a true callous peptic ulcer has formed, its biology may proceed in various directions.

THE BIOLOGY OF PEPTIC ULCER




1. *Healing.* Superficial ulcers may heal without leaving a trace, but if the ulcer has penetrated beneath the muscularis mucosae, it is hardly likely that such an ulcer may heal without scar formation. Such scars are fairly common at necropsy examination in individuals who have previously had clinical peptic ulcers. The results of excessive scarring resulting especially in either dilatation or hour glass stomach are familiar. Clinical healing however is not always synonymous with anatomical healing. A patient may feel well with persistent niche or crater sometimes for months, after he has been "cured". The persistence of the ulcer is only one of the factors that renders peptic ulcer so subject to recurrence. Recurrence is frequent enough even after the ulcer has roentgenologically disappeared. The reason for the notorious recurrence is that one cannot divorce the human equation. Reports of "cure" of peptic ulcer by any method of therapy even after an interval of years are therefore to be viewed with reserve. In view of the basic conditioning factor of acid in the production of both peptic and jejunal ulcer, the one hope of obtaining a permanent cure is by creating a permanent achlorhydria. Thus far, only surgery in the form of subtotal gastrectomy has succeeded in this aim, but unfortunately only in a measure. It is well agreed that an achlorhydria is more likely to be attained if the ulcer is gastric rather than duodenal. In what percent a permanent achlorhydria results in both types of ulcer has not yet been determined, because the period of observation is still too short. Peptic ulcer has a long biological cycle.

2. *Hemmorrhage.* The amount varies from one that gives only the reaction for occult blood in the stool to those sufficiently large to give profound systemic reactions. These arise frequently after psychological trauma (30, 31).

3. *Perforation.* Perforation usually occurs into the general peritoneal cavity or into the lesser sac. Occasionally, if slow, it may localize in the subphrenic space. Rarely, the perforation passes into another abdominal viscus usually the colon.

4. *Carcinomatous degeneration.* The reports of the incidence of cancerous change vary widely according to the criteria employed. In some clinics it is as high as 30 per cent, and with such a high incidence, these observers advocate complete resection of all peptic ulcers as a prophylactic measure. The report of

such a high incidence is largely due to the interpretation of heterotopic proliferation of the mucosa at the edge of an ulcer as a malignant change. Using strict morphological criteria, Klein (31) subjected a series of 141 cases of peptic ulcer and 353 cases of gastric carcinoma to a careful critical review and found only two that could be considered as carcinomatous transformations of a peptic ulcer. Under any circumstances, the determination of such a change is sometimes difficult.

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CHAPTER 17

# ACHLORHYDRIA IN RELATION TO ANEMIA

The term "achlorhydria" represents an absence of hydrochloric acid in the stomach while "achylia gastrica" implies in addition the absence of pepsin. For clinical purposes this distinction is of insignificant importance.[1] There is probably no congenital achlorhydria. In 55 newborn unfed infants, Hess (1) found as much as 10 cc. stomach contents with acidities of normal range. Hawksley, Lightwood and Bailey (2) found hydrochloric acid in all healthy infants after the fourth week of life. However, it is generally agreed that the incidence of achlorhydria increases with age (Conner (3), Bockus, Bank and Willard (4)), so that by the seventh decade the incidence is close to 30 per cent. In those suffering from gastric complaints, Conner (3) found an average of 15.2 per cent. The general average in health varies with the method used. Bockus, Bank and Willard (4) using histamine and a two hour method found an average of 5.7 per cent. Winkelstein's (5) percentage using both histamine and neutral red was 2.2 per cent and when he excluded cases of pernicious anemia, carcinoma, gall bladder disease and Graves' syndrome, the average was 1.2 per cent which represents what he terms "essential" achlorhydria.

There is a remarkable familial and hereditary tendency to acquire achlorhydria. This was disclosed in the study of the incidence of achlorhydria in blood relatives of patients who suffered from pernicious anemia. Thus Conner (3) found that the incidence including all decades was 25.9 per cent and that there was a progressive incidence with age, so that by the seventh decade the incidence was 57.1 per cent. In not a single incidence did achlorhydria occur before the age of 10 years. Wilkinson and Brockbank's (6) figures are practically identical with those of Conner, 24.1 per cent. Whether this tendency follows the Mendelian law and whether it is dominant or recessive, can only be determined by observations on families in whom the disease occurs in three or more generations, and inasmuch as pernicious anemia usually develops only in middle age, such observations would require a long period of follow-up. The significance of these data in relation to pernicious anemia will be discussed later.

In all likelihood, the development of achlorhydria is not sudden but gradual.

[1] In this discussion we shall refer only to true achlorydrias, i.e., where no hydrochloric acid is found after stimulation with histamine.

Bockus, Bank and Willard (4) noted the gradual decrease in acid to disappearance in a few of their patients.

Martius, many years ago, regarded the achlorhydria as primary and constitutional, but, largely sponsored by Faber (7), and since encouraged by gastroscopists, most current writers ascribe the achlorhydria as secondary to a "chronic atrophic gastritis." Faber found extensive round cell infiltration, with progressive atrophy of the mucosa, fibrosis, cystic dilatation of the gastric glands and a metaplastic conversion of portions of the mucosa to the intestinal type. Brown (8) found in 37 of 42 cases of pernicious anemia a disappearance of the acidophilic cells and in 41, a chronic gastritis similar to that described by Faber. In 20 of the cases which had received therapy, the histologic picture was unchanged. In eight autopsies on patients with pernicious anemia, Meulengracht (9) found a gastritis in the fundus of the stomach with disappearance of the acid and chief cells, but little or no change in the pylorus. He found difficulty in reconciling these findings with his previous observation (9) that in pigs the antianemic or intrinsic factor is found in the pylorus and neighboring duodenum (pyloric gland). This discrepancy has since been solved by Fox and Castle (10) who while confirming Meulengracht's work on the stomach of the pig have found that in the human being the fundus and cardia and not the pylorus contain most sites for the formation of the intrinsic factor. The work of Fox and Castle also serves as the explanation for the rarity of pernicious anemia after resections of the stomach, even when only a small portion of the fundus is left *in situ*. On the other hand, Magnus and Ungley (11) found no evidence of a gastritis in pernicious anemia, but an atrophy of all the coats of the stomach. The mucosa was represented by a surface epithelium with a few scattered glands lined by mucus producing cells, while the oxyntic and peptic cells disappeared. In several stomachs they also found areas of metaplastic intestinal epithelium. There was no involvement of the pyloric region or of Brunner's glands.

Any discussion of the relation of atrophic gastritis to achlorhydria with or without pernicious anemia is inevitably linked up with the relation of gastritis, whether atrophic or hypertrophic, to other diseases. It seems that there has been an uncritical acceptance of these morphologic changes as indicative of diseased gastric states without taking into consideration whether these changes may be the result of the normal involution of age. Hamperl (12) and Hillenbrand (13) found a high incidence of chronic gastritis in patients in later life who were free from gastric complaints. Hebbel (14) in autopsy material on similar individuals found hypertrophic gastritis of any degree rare below the age of thirty, and severe changes uncommon after the fiftieth year, while atrophic gastritis was exhibited in 30 per cent of 108 cases past the age of fifty. Benedict and Mallory (15) regard the hypertrophic gastritis as an exaggeration of the physiologic plasma celled and lymphocytic infiltration of the normal stomach.

Gastroscopy has not helped in the solution of the problem because there has been insufficient correlation with histology. In the few studies that have been thus far reported, there has been only an approximate confirmation. Thus Swalm and Morrison (16) report that gastroscopy only corroborates the clinical

findings in 52 per cent of their cases, while on the other hand, chronic gastritis may be present with a normal gastroscopic picture. In 25 per cent of their cases the gastroscopic appearance of a mild, moderate or chronic gastritis was contradicted by the histologic examination. Benedict and Mallory (15) in a study of resected stomachs showed complete agreement between the gastroscopic and histologic findings in 54.9 per cent and partial agreement in 33 per cent. There was no correlation in 11.8 per cent. The pathologist and the gastroscopist were fairly well agreed in the diagnosis of atrophy. Further unbiased studies on such correlations are much to be desired.

The concept of chronic atrophic gastritis as the cause of achlorhydria is confronted with some irreconcilable clinical facts concerning achlorhydria and pernicious anemia. Aside from the undefined nature of the lesion as an inflammation, according to accepted criteria, this concept does not explain the following observations: 1) The comparative absence of achlorhydria and pernicious anemia before puberty; 2) their familial and hereditary character; 3) the restoration of the gastroscopic picture of atrophic gastritis to normal after specific therapy was instituted (Schindler, Kirsner and Palmer (18)). Whether this gastroscopic transformation is only one of appearance or represents a histologic restitution is only answerable by a before and after biopsy. To complicate matters, Schindler and his co-workers (18) found that in 5 per cent of patients with complete anacidity proven by histamine the mucosa of the stomach was gastroscopically normal. 4) The occasional gastroscopic picture of hypertrophic gastritis in achlorhydria (Winkelstein (5) 2 out of 14 cases). The fact that no assignable cause for the development of the atrophic gastritis can be ascribed is in favor of the primary nature of the achlorhydria. The problem as to whether the achlorhydria is primary or secondary may be solved by studying the histology of the stomach in patients in whom a complete achlorhydria has been attained, for instance, by partial gastrectomy. Thus far, such a study has, as far as I am aware, not been pursued.

A. *Relation of achlorhydria to idiopathic hypochromic anemia.* Idiopathic hypochromic anemia is a syndrome that affects mostly women of middle age and is characterized by weakness, pallor, atrophy of the tongue, brittle finger nails and an enlarged spleen. The anemia is not attended by any evidences of hemolysis. The Plummer-Vinson syndrome is an occasional accompaniment. These patients respond promptly to the administration of iron but not to liver. Nearly all possess a complete achlorhydria as attested by histamine. Wintrobe and Beebe (20) determined this in all of 12 patients. Castle and Minot (21) found achlorhydria in 25 out of 30 individuals, Damashek (22) in 14 out of 17. Castle, Townsend, and Heath (23) found the intrinsic factor invariably present in hypochromic anemia. This is of special significance in view of what we shall soon discuss, namely, the occasional transition of idiopathic hypochromic anemia into true pernicious anemia.

The gastroscopic picture of atrophic gastritis has been reported in hypochromic anemia. In one case reported by Schindler, Kirsner and Palmer (18), the gastroscopic picture was restored to normal by iron. Schiff and Goodman (24) report a similar observation.

The prevailing view of the pathogenesis of hypochromic anemia is based on the observations of Mettier and Minot (25) who showed that in idiopathic hypochromic anemia, the response of the bone marrow to iron is greater when the contents of the upper intestinal tract are slightly acid than when it is alkaline. Minot and Castle (21) in addition, suggest that the widespread changes in the intestinal tract as reflected in the glossitis, may interfere with the absorption of iron and they cite the observation of Singer and Wechsler (26) who found inadequate absorption of galactose in achylic states. Its preponderance in women is ascribed to the loss of blood during menstruation which acts as a conditioning factor. Other losses of blood, for instance from hemorrhoids (Bloomfield (27)) may act in a similar manner.

The probability is strong that hypochromic anemia is not a disease, because it has altogether too many backgrounds. It may be associated with sprue, pregnancy, myxedema and may arise after gastroenterostomy or partial gastrectomy. Bloomfield (27) holds that hypochromic anemia and chlorosis have so many clinical features in common as to be indistinguishable.

B. *The relation of achlorhydria to pernicious anemia.* That an achlorhydria is an almost ever present association in pernicious anemia is acknowledged except in rare instances (Castle, Heath and Strauss (28)). It is now well accepted that the achlorhydria antedates the onset of the anemia, sometimes by many years (for references see Moschcowitz (29)). Moreover, the achlorhydria never returns despite restoration of the blood picture by specific therapy. There is ample testimony that pernicious anemia is often familial and hereditary (Moschcowitz (29)), sometimes occurring in three generations, and this is reflected in the frequency in which achlorhydria is found in blood relatives of individuals affected by pernicious anemia (Conner (3), Wilkinson and Brockbank (6)). It is evident therefore that achlorhydria is a significant conditioning factor for the production of pernicious anemia and this is confirmed by the reports of pernicious anemia that occasionally follow complete gastrectomy (Finney and Rienhoff (30)). However, the causative relation between achlorhydria and pernicious anemia is not absolute because achlorhydria may be persistent for as much as seven years without the development of pernicious anemia (Bloomfield and Polland (32)) and pernicious anemia may develop in an individual with hydrochloric acid in the stomach. The problem was largely clarified by the classic work of Castle who showed that in pernicious anemia there was an absence of an intrinsic factor. The intrinsic factor is not pepsin, although the two are in a measure associated (Davies (33)). The absence of an intrinsic factor in pernicious anemia seems constant, because as Castle, Heath and Strauss (28) have shown, it was absent in pernicious anemia with normal gastric juices and in achylic individuals without an anemia or with hypochromic anemia.

C. *The transition of idiopathic hypochromic anemia to pernicious anemia.* The common association of some of the clinical phenomena in both conditions, notably the anemia, the atrophy of the tongue and the achlorhydria would suggest that the two are related and such indeed is the case, for there are ever increasing reports of the transition of idiopathic hypochromic anemia to pernicious anemia

(Castle and Minot (21), Witts (34), Davies (33), Heath (35), Gram (36), Damashek and Miller (37)). Apparently the transition is not sudden because all of these observers report cases where clinical features of both are combined, for instance, pernicious anemia with a low color index, subacute combined degeneration of the spinal cord with a hyperchromic anemia (Witts (34)). In this category may be classified the cases of pernicious anemia who require iron to maintain a normal blood level (Beebe and Lewis (38), Heath (35)). In all likelihood, this transition is more common than the reported cases indicate and it is by no means improbable that many patients with pernicious anemia pass through a hypochromic stage, but this phase is hidden from us because the patient is not examined until the blood picture is full blown. This transition also accounts for the not infrequent reports of a familial idiopathic hypochromic anemia in the blood relatives of patients with pernicious anemia (Davies (33), Damashek (22), Heath (35), Witts (34), Conner (3), Mustelin (39), Patek (40), Gram (36)). Faber and Gram (41) describe a family of three generations in whom most of the members were afflicted with either pernicious or idiopathic microcytic anemia.

It seems remarkable that these two conditions that are biologically identical should respond entirely differently to the two specific remedies, liver and iron, even though there are borderline cases in which both are effective when given simultaneously. The precise mechanism is not known. Hurst (42) speculates that the atrophic process begins in the proximal half of the stomach when acid is excreted and later involves the pylorus and duodenum. Inasmuch as the intrinsic factor of Castle has thus far never been found in pernicious anemia and always in hypochromic anemia (Castle, Townsend and Heath (43), Hartfall (44)), it is reasonable to infer that the transition is due to the disappearance of this factor. The spontaneous biologic course is always in the direction of hypochromic to pernicious anemia and not reversely.

D. *Relation of achlorhydria to the anemia of pregnancy.* The work of Strauss and Castle (45), has clarified considerably our knowledge. In 24 pregnant women, they showed that 75 per cent did not secrete the normal amount of hydrochloric acid during more than half the period of pregnancy. Three patients had achlorhydria which did not return after delivery. After delivery the average secretion was three times as great.

Hypochromic anemia in pregnancy occurs during the last trimester and is ascribed to the demands of the growing fetus, plus dietary insufficiency and is especially conditioned by achlorhydria or hypoacidity, or a related gastrointestinal disturbance. This form of anemia is usually relieved by iron. Occasionally, the anemia of pregnancy is macrocytic; this occurred in 6 out of 36 pregnant women with anemia, and in all the intrinsic factor was lacking. But the macrocytic anemia of pregnancy differs from pernicious anemia in that there may be no relapse after recovery, although liver is not administered; and furthermore, achlorhydria was only found in two of the six cases. In one, the acid returned two years later. Strauss and Castle suggest that in the macrocytic anemia of pregnancy there may be a combined deficiency of liver and iron, as proven by one of their cases. They also suggest that in the macrocytic anemia,

as in true pernicious anemia, there is a lack of both the intrinsic and extrinsic factors. In other words, in the anemias of pregnancy, similar mechanisms are at play as in idiopathic hypochromic anemia and in pernicious anemia. While the majority of pregnant women with macrocytic hypochromic anemia are cured after parturition, some require persistent treatment with specific measures. These represent accidental associations of pregnancy and pernicious anemia.

E. *The relation of achlorhydria to the anemia or sprue.* Tropical and non-tropical sprue have so many clinical characters in common that for our purpose they may be discussed together. In tropical sprue, Castle and Rhoads (46) found achlorhydria as tested by histamine in 30 per cent; in non-tropical sprue (Snell (47)) found achlorhydria in about 35 per cent (in six of the eight cases tested by histamine). Whether the hypoacidity that is so common in sprue, especially in the early stages, is evidence of a tendency to achlorhydria is unknown. In both tropical and non-tropical sprue both a hypochromic and a macrocytic hyperchromic anemia occur. In 22 cases of non-tropical sprue Snell found a hypochromic anemia in 5 and a macrocytic hyperchromic anemia in 17. Castle and his co-workers (48) regard the mechanism of the development of the macrocytic anemia in sprue as analogous to that of pernicious anemia. In other words, there is a failure in reaction between the extrinsic factor associated in many instances with vitamin $B_2$ (G) and an intrinsic factor. In addition, there is difficulty in absorption of substances from the intestinal tract resulting from this failure in the hematopoetic reaction. In one patient who died of sprue and macrocytic anemia, the liver contained no detectable hematopoetic principal. Thus the macrocytic anemia of sprue arises from the variable participation of three defects, the extrinsic factor, the intrinsic factor and absorption. Also as in pernicious anemia, the administration of liver, especially parenterally, is usually effective and in certain instances, as in pernicious anemia, iron must be added. The parallelism was further maintained by the experimental production in swine of a disease akin to sprue by feeding a modified canine black tongue diet (Miller and Rhoads (49)). They obtained a symptom complex marked by oral manifestations, achlorhydria and an anemia which is usually macrocytic but may be microcytic. The disease is associated with a loss of the intrinsic factor both in the stomach and in the liver. The achlorhydria preceded the anemia in every instance. The disease responds to liver extract but not to iron alone. The one important difference is the return of the hydrochloric acid in the experimental animals.

F. *The relation of achlorhydria to the anemia of myxedema.* The usual anemia that is associated with myxedema is normocytic or microcytic responding to thyroid, but a number of observers have reported a hyperchromic macrocytic type resembling that of pernicious anemia which requires the administration of liver in addition to thyroid (Means, Lerman and Castle (50) (5 cases), Davis (51) (1 case), Hölböll (52) (3 cases), Lisser (53) (1 case)). In Means, Lerman and Castle's cases, the pernicious anemia preceded the development of the myxedema in three instances, followed the myxedema in one, and in the other the sequence could not be determined. All these observers report an associated achlorhydria.

Lerman and Means (54) found an achlorhydria in 53 per cent of their cases of myxedema. Golding (55) found the gastroscopic picture of mucosal atrophy in 10 of 11 cases, in one confirmed by histology. The lowered metabolic rate is especially significant because, as a rule, the rate in pernicious anemia is in the upper limits of normal (Myers and Dubois (56)). It is hardly likely that the association of pernicious anema and myxedema is accidental in view of the comparative high incidence.

G. *The relation of achlorhydria to the anemia of gastric carcinoma.* The only significant relation we need discuss is that of pernicious anemia. The problem centers around three possibilities: 1) whether pernicious anemia with its achlorhydria acts as the soil upon which the carcinoma is engrafted (Hurst (57)); 2) whether the pernicious anemia results because of the achlorhydria engendered by the cancer; and 3) whether both diseases are accidentally associated. Doehring and Eusterman (58) report from the Mayo Clinic 40 cases of pernicious anemia associated with gastric carcinoma out of 1,014 cases of pernicious anemia admitted between the years 1935–1939 which is an incidence of 1.7 per cent, slightly higher than the incidence of gastric carcinoma in the general population. They very reasonably discuss the possibility that the age incidence of pernicious anemia has been prolonged in recent years through specific therapy which accounts for the increasing frequency with which this association has been noted in the Mayo Clinic. In 26 of the 40 cases the pernicious anemia clinically preceded the cancer, in 12 it was simultaneous and in 2 the carcinoma preceded the pernicious anemia. These sequences do not decide much because of the notorious dormant nature of both maladies. The fact that the anemia so often responds to liver treatment also does not help in the solution.

There is no reason to believe that every achlorhydria leads to either anemia or other disease. Bloomfield and Polland (32) have followed over periods of one to seven years the fate of 45 patients in whom achlorhydria was found casually and in not a single one did any form of anemia or gastric carcinoma develop. Aside from the fact that even seven years is not a sufficient period of observation, it must be remembered that the development of the anemia is conditioned by other factors, notably, menstruation, loss of blood, intestinal absorption and above all, deficiency in the extrinsic substance. Only a far enough future with strict observation can decide this aspect of the problem.

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CHAPTER 18

# CARDIOSPASM

*Etiology.* Although older writings are full of references to the "hysterical" and "neurotic" personality of affected individuals and to the frequency of a psychic trauma in the initiation of the cardiospasm, the psychosomatic nature of the malady was not seriously considered until comparatively recent times. Thieding (1) in 1921 was apparently the first to suggest a psychological origin since he was struck by the frequency with which it followed a psychic trauma, and that it occurred especially in individuals with neuroses. In 1926 Schindler (2) subscribed to this view and was enabled to cure early cases by psychotherapy. He also observed that the disease frequently followed an annoyance that "had to be swallowed," usually from somebody superior. Alkan (3) writes in a similar vein, and notes that relapse frequently follows some excitement. Winkelstein (4) reported 8 cases of cardiospasm following a psychological trauma; in two instances cure followed psychotherapy. He regarded cardiospasm as an exquisite example of an organic disease of functional origin. In the discussion of Winkelstein's paper Verbrycke (5) quotes the case of a patient who was relieved by dilatation but the cardiospasm recurred immediately following the robbery of his bank. Frey and Duschl (6) view cardiospasm as an organ neurosis following various forms of psychological strains, and believe that psychotherapy may effect a cure in early cases. Opitz (7) expresses himself similarly. Weiss (8) recently stressed the psychosomatic nature of cardiospasm and reported nine cases. He finds that cardiospasm follows an emotional conflict; that it often occurs during puberty in persons whose early life gives evidence of personality difficulties. Other members of the family are often neurotic. Parent-child and sibling relationships are seriously disturbed. Exacerbations occur which can be frequently correlated with fresh psychic insults. Weiss views the physical disorder as representing symbolically a compromise between the gratification of certain impulses and their rejection by another part of the personality. He holds that the malady necessitates both physical and psychological treatment. The latter is especially useful in early cases and as an adjuvant in the later phases.

As further testimony of the psychosomatic nature of cardiospasm we may cite the frequency with which cardiospasm is associated with other psychosomatic diseases. Of 42 cases collected from the records of the Mount Sinai Hospital,

four or 9.5 per cent were associated with peptic ulcer, usually near the cardia, two or 4.8 per cent with Graves' syndrome, one or 2.4 per cent with mucous colitis and one or 2.4 per cent with essential hypertension. The comparatively high incidence of cardiospasm with peptic ulcer is noteworthy, and has been frequently commented upon. Such cases are viewed generally as "secondary" cases of cardiospasm as contrasted to the primary variety in which "no cause" could be assigned, and is viewed as reflex in origin. We question whether this view is correct, since in a few cases that have come under our observation, the patient states that the spasm arises from fear that the ingestion of food may cause pain or distress.

Cardiospasm is the only psychosomatic disorder that occurs comparatively frequently in children and even in sucklings and this fact has been used as a refutation of its psychosomatic nature. Nevertheless the literature of pediatrics contains abundant testimony that cardiospasm frequently follows psychological trauma. Husler (9) reports and quotes a number of cases in which the cardiospasm promptly followed weaning either to the bottle or to solid food. He frequently observed this occurrence in spoiled, unruly and tyrannical children whose parents are neurotic and are protective. The child is often the only child. Treatment by suggestion or through circumspect handling of the mother is usually efficacious. Sudhues (10) collected 101 cases in children below the age of 13. Most occurred during the first or second year, and he regards cardiospasm as one of the commonest causes of vomiting in early life. He found that a large percentage of the parents were of the neurotic or hysterical type and that the older children frequently suffered from enuresis and pavor nocturnus. Lust (11), Monrad (12) and Finkelstein (13) describe cases of cardiospasm in children following suggestion incited by indiscreet remarks of parents or the insistence on their part to eat disliked foods, or a food that previously had caused some distress. These children recovered by suggestive treatment or some other form of psychotherapy. Lust reports the case of a child of 3 that was cured by hypnosis. Kelly (14) describes a number of children with cardiospasm due to psychic trauma.

The frequency of cardiospasm in infants and children is probably due to the fact that oral receptivity plays a much larger role in their motivation than it does in adults.

Cardiospasm like most psychosomatic disorders, especially Graves' syndrome and peptic ulcer, is much more frequent during wars. Abel (15) and Meyer (16) saw a large number during World War I, and Hoffman (17) observed it frequently in camps during World War II.

Inasmuch as we believe that all psychosomatic diseases are the result of two factors, namely the impact of a psychic insult upon a psychological background or constitution it would be fruitful to study the type personality that is subject to cardiospasm. Our own experience has not been sufficient to warrant a definite statement, but from our limited experience they are fearful, sensitive and extremely insecure folk who approximate the type we have previously described

as characteristic of Graves' syndrome (18). They are subject to tremors under stress, dermographia, increased sweating and turgidity of the skin. Abel and Thieding have made similar observations.

There can be little doubt that cardiospasm represents an achalasia (19) that is, the failure of the relaxation of the normal tonus of the cardia before the advancing food. The probability is also strong that this is mediated through the autonomic nervous system, but this is not equivalent to saying that the cause of cardiospasm is a dysfunction of this system, a statement frequently made. Changes in the vagus nerve have been reported by some observers, and none by an equal number. In late cases, changes in the sympathetic ganglia of the walls of the esophogus have been reported, but these are believed to be secondary, due to the profound inflammatory changes within the esophogus.

It occurs about equally in both sexes.

*Course.* As in Graves' syndrome, the cardiospasm may arise suddenly, as after a fright, or gradually, from a slow continuous or reiterating anxiety. At first, the spasm is intermittent; later the periods of well being become shorter and shorter, until finally the spasm is persistent, and the victim finds it increasingly difficult for food to enter his stomach. In this stage fluoroscopy shows a slight diffuse fusiform or spindle-shaped enlargement of the esophogus, with a slow trickle-like emptying of the barium into the stomach; and treatment by suggestion, psychotherapy or even hypnotism may afford complete relief. If the process continues, the dilatation becomes progressive from below, upward, and it becomes more marked in the lower two thirds of the esophogus. The patient now finds that only by forcible movements of the chest muscles can he force food into the stomach. This exertion causes pain in the lower part of the chest. In a still later stage the esophogus not only continues to dilate but lengthens forming an S shaped curve, with the redundant portion becoming so large as to fold upon the diaphragm or it may even invaginate through the diaphragm into the stomach. The esophogus in the advanced phases may hold as much as 500 cc. of fluid and under such circumstances may compress the surrounding mediastinal structure sufficiently to cause asthma-like symptoms.

Morphologically, the esophogus in the early stages is entirely normal with the exception of the moderate dilatation. In the advanced stages, there is a profound thickening of the muscular coat especially of the circular layer, which undoubtedly represents a work hypertrophy. Furthermore as the result of the stagnation of food content, inflammatory changes in the wall of the esophogus occur with edema of the mucosa and not infrequently superficial mucosal ulcerations or deep ulcers. Perforation is very rare, but lymphangitic extension of the inflammatory process may cause a chronic mediastinitis or a mediastinal abscess. Carcinoma develops in cardiospasm more frequently than the normal average, according to Fleiner (20) in 7.5 per cent. Chronic pneumonitis (21) or bronchiectasis or lung abscess (22) from aspiration of food are not infrequent. At operation or autopsy no closure at the cardiac opening is found. This only occurs during life.

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CHAPTER 19

# SPRUE SYNDROME

This syndrome comprises a number of allied disorders that have been variously termed coeliac disease, Gee-Herter disease, Gee-Herter-Thaysen disease, tropical sprue, non-tropical sprue, tropical macrocytic anemia and idiopathic steatorrhea. Any attempt at precise definition between these disorders must necessarily be an artificial one since they largely represent phases or symptom complexes without a precise or uniform etiology or a consistent background in morbid anatomy. From a pathologic-physiological viewpoint there is an extraordinary overlapping. Furthermore, these disorders may give rise through intermediary mechanisms to other symptom complexes in whole or in part, notably pernicious anemia and pellagra. For these reasons, it is highly essential, as Snell (1) points out, to visualize these disorders from the biological rather than the static viewpoint.

In order that we may orient ourselves concerning the conventional nosology of these terms, coeliac disease and Gee-Herter disease are synonymous and represent the sprue syndrome that arises in childhood. The Gee-Herter-Thaysen disease is synonymous with non-tropical sprue and represents the type that occurs in adults. Tropical sprue is identical in every respect to non-tropical sprue; its greater incidence in the tropics is due to the greater incidence of dietary insufficiency consequent upon living in a hot climate. "Idiopathic steatorrhea" is an indifferent term that covers a host of unrelated conditions in which steatorrhea is the main symptom. It is no longer "idiopathic" since it has a number of backgrounds in morbid anatomy, such as pancreatic disease, intestinal stricture and fistulae, obstruction of the intestinal lacteals, and Whipple's intestinal lipodystrophy.

Tropical macrocytic anemia resembles sprue in every particular except for the fact that it is relieved by yeast which contains a substance closely allied to the intrinsic factor of Castle, while sprue requires liver in addition (2). Inasmuch as Miller and Rhoades showed experimentally in swine that, by omitting the extrinsic factor, they produced a loss of intrinsic factor followed by a macrocytic anemia which responded to liver, one has reason to believe that tropical macrocytic anemia represents the early phase of the sprue syndrome, and that the difference between the two is quantitative rather than qualitative. In fact,

the sprue syndrome does not spring into being fully matured. So-called larval or incomplete types have been reported, aside from the macrocytic anemia just described (3, 4, 5). That these larval forms are by no means infrequent is evident from the report of Manson-Bahr and Willoughby (5) who found 22 such instances in 200 cases of sprue. These larval or incomplete types comprise various signs and symptoms; glossitis, weight loss and anemia without intestinal signs, etc. Hanes (4) in reviewing 77 cases of pernicious anemia discovered three that were eventually diagnosed as sprue. Some reports of pernicious anemia without achlorhydria represent in his opinion early forms of sprue.

*Etiology and pathological physiology.* The etiology of the sprue syndrome was almost entirely conjectural until the fundamental observations of Castle and his coworkers (3) in Porto Rico. They found in fully developed cases a deficiency of the extrinsic factor and in most instances a deficiency of the intrinsic factor. According to Miller and Rhoades (2), the sequence of events appears as follows. As a consequence of the loss of intrinsic factor an inflammatory change in the gastric mucosa occurs as manifested by a glossitis and stomatitis. This first stage is not usually associated with either achlorhydria or anemia. As the disease progresses, atrophy of the gastric mucosa occurs, with resulting achlorhydria and a loss of the hematopoietic activity of the gastric juice; this is followed by anemia, which is usually hyperchromic and macrocytic in type, identical to that of pernicious anemia. Experimentally Miller and Rhoades reproduced the sprue syndrome in swine by administering Goldberger's diet which produces the black tongue disease in dogs characterized by stomatitis, hypochromic anemia, glossitis, diarrhea and prostration. Inasmuch as dogs are not amenable to the experimental production of the sprue syndrome, because the stomach does not contain the hematopoietic agent and the liver is low in the anti-pernicious anemia principle, they employed swine. They produced achlorhydria, macrocytic and microcytic anemia and diarrhea. The achlorhydria preceded the anemia in every instance. Neither the gastric secretion nor the liver contained the anti-anemic principle. The achlorhydria, interestingly enough, persisted in all but one of the animals. At autopsy they found atrophy of the gastrointestinal mucosa.

In sprue, as in pernicious anemia, there is a failure in reaction between the extrinsic and intrinsic principles. In addition, the difficulty of absorption of substances from the intestinal tract resulting from failure of this hematopoietic reaction is probably present in certain instances of both diseases. The essential difference between sprue and pernicious anemia is, that in sprue the achlorhydria is acquired, apparently due to prolonged loss of the extrinsic principle, while in pernicious anemia the evidence is strong that the achlorhydria and the subsequent loss of the intrinsic principle are the result of a familial and genetic factor (6). In both diseases the extrinsic principle acts as the agent that leads to deficiency, for Castle and his coworkers have shown that in most cases of fully developed sprue, liver, especially parenterally administered, is quite as specific as in pernicious anemia. In tropical sprue, the loss of the extrinsic factor is ascribable to the deficient diet of the natives and northerners in the tropics. Ashford (7)

who had an unusually extensive experience in Porto Rico, comments on this fact. The food in tropical climes is insufficient in hematopoietic substances; moreover, the high temperatures subconsciously impel one to choose carbohydrates and fat as the main sustenance. Among the natives, poverty is a factor in such a choice. In non-tropical sprue as well, the history of a previously deficient diet is extremely common (1, 4). The primary loss of the extrinsic principle and later of the intrinsic is paralleled in the corresponding responses to treatment. In the early stages, sprue is often relieved by the vitamin B complex alone; in the later phases liver was necessary. Liver cured even the so-called abortive or incomplete cases, showing that such evidences are not necessarily always early phases of sprue. The presence of acid in the stomach did not necessarily imply that the intrinsic principle was present. Castle and his coworkers found a histamine tested achlorhydria in 31 per cent of all cases, a percentage approximate of that found by Hanes (4). Hanes showed that the acid sometimes returns after treatment, and if hypoacidity was present previously, that the acid rose. Whether the microcytic hypochromic anemia often found in sprue is related to the presence or absence of achlorhydria and indirectly to the presence or absence of the intrinsic factor, is not certain, but the fact that a microcytic hypochromic anemia is practically the rule in coeliac disease of children (8), in whom a complete achlorhydria after histamine never occurs (9, 10), suggests such an association. As far as one can determine, the intrinsic factor has never been determined in the coeliac disease of children. On the other hand, the hypochromic microcytic anemia may represent a phase in the development of the hyperchromic macrocytic variety. Thaysen (11) found that the anemia is of the hyperchromic variety during the active stage of sprue and is hypochromic during the remission. This same phenomenon occurs at times in true pernicious anemia (12, 13). In immediate relatives of patients with pernicious anemia, some show hyperchromic and other hypochromic anemia. Heath (13) was able to convert one type into another by giving either liver or iron over a prolonged period. In pernicious anemia it is sometimes necessary to add iron to liver therapy to fully restore the anemia (3). Castle and his coworkers (3) found similar changes in sprue; after giving liver, the blood picture sometimes changed to the hypochromic type and it was necessary to add iron. Finally, a hypochromic anemia in sprue may, in part, be the result of deficient absorption of hematopoietic substances. Mettier and Minot (14) have shown that such substances are poorly absorbed in the absence of hydrochloric acid in the stomach. The parallelism between sprue and pernicious anemia is further emphasized by the absence of the hematopoietic substance in the liver (3) and the occasional association in sprue of combined sclerosis of the spinal cord (4, 3, 15). Castle and his coworkers found such evidences in 8 of 92 cases of sprue. In summary, this discussion of sprue from the dynamic aspect reveals that a malady, pernicious anemia, whose nosology has heretofore been regarded as more or less sharply defined, has been engrafted, and it is only by a knowledge of the sequence of events that one is enabled to differentiate one from the other. Even the bone marrow in both conditions are identical (3). Of course, it is possible that some

patients may have been individuals with a potential pernicious anemia, and who, under altered dietetic conditions, developed simultaneously the sprue syndrome and pernicious anemia, but this circumstance must be very exceptional, to say the least.

*Relation of coeliac disease to the sprue syndrome of adults.* Coeliac disease of childhood is clinically identical to that of adults except in two particulars. 1. While hypoacidity is common and achlorhydria less so in coeliac disease, true achlorhydria after histamine never occurs (8, 10). 2. The anemia is nearly always of a hypochromic type (8, 10, 16, 17). These two components, in all probability, are related, inasmuch as all evidence indicates that a hyperchromic megalocytic anemia cannot develop in the absence of a true achlorhydria, in which an absence of intrinsic principle is more likely to occur. Unfortunately, there are no studies available on the determination of the intrinsic principle in coeliac disease of children. Recently, May, McCreary and Blackfan (17) conceiving that coeliac disease represents a deficiency disorder as in adult sprue, administered crude liver extract and the vitamin B complex with striking results, obtained within a period of 3 to 6 weeks of treatment, as shown by a normal absorption of vitamin A, the restitution of a normal glucose tolerance curve and a profound improvement in the general condition and well being of the patients. It seems strange that this concept had not been considered before. They found that either crude liver extract or the vitamin B complex alone was not sufficient. This observation suggests strongly that similar circumstances as regards the relations between the intrinsic and extrinsic principles will be found in coeliac disease. As in adult sprue a frequent history of dietary deficiency is obtained. Coeliac disease usually begins at the end of the first year of life. Although, hyperchromic anemia in coeliac disease of childhood is rare, it does occur. In Parsons' (8) experience, the hyperchromic type was only found in prolonged or neglected cases. That coeliac disease and adult sprue are identical is suggested by the frequent history of transition from one into the other. Time and again in perusing the histories of reported cases of adult sprue, one finds that the disease already began in childhood or even infancy (18, 1, 19, 20, 4, 21, 22) with greater or lesser periods of remission in between.

*Gastrointestinal insufficiency as related to the sprue syndrome.* The sprue syndrome comprises various other phenomena aside from the changes in gastric secretion and the anemia, that are in a large measure ascribable to deficiency in absorption from the gastrointestinal tract. We refer to the diarrhea, anorexia, emaciation, meterorism and eventually a protuberant abdomen, steatorrhea, hypocalcemia and hypophosphatemia, a flat sugar tolerance curve, a hypoproteinemia, avitaminosis and inability to visualize the gall bladder by oral administration of dye (23). All observers agree that there are no gross postmortem changes in the gastrointestinal tract in the sprue syndrome except thinning of the mucous membranes; and inasmuch as there is complete reversibility with complete restoration of the normal powers of absorption after appropriate treatment, one must conclude that the defective function is directly traceable to the primary etiological defect, namely the failure of interaction between the

extrinsic and intrinsic factor. In other words, this deficiency is an intermediary mechanism which in turn gives rise to the clinical phenomena enumerated above. We will discuss these phenomena in order.

a. *Diarrhea.* Although diarrhea with large foamy and fatty stools are characteristic of sprue, these attributes are not always present (4). b. *Steatorrhea.* In 48 cases of sprue Hanes (24) found that the average amount of fat in the dried stool was 48.5 per cent as compared to the normal which does not exceed more than 15 percent. The steatorrhea is due to defective absorption and is independant of pancreatic insufficiency because in sprue, lipase in the intestinal tract is sufficient. The mechanism of the insufficient absorption of fat is not clear. Barker and Rhoades (25) and Adlersberg and Sobotka (26) found in sprue no increase in blood lipoids after a fatty test meal, and after giving liver parenterally they found a post absorptive blood level which approached the normal. c. *Calcium deficiency.* The low blood calcium in sprue is the result of a number of factors. 1. The steatorrhea results in an excessive formation of fatty acids which combine with the calcium in the intestine to form insoluble soaps which are carried off and thus results a negative calcium balance. 2. The steatorrhea interferes with the absorption of the fat soluble vitamin D. The low calcium, especially of the ionized fraction, leads to occasional tetany, and together with the comparatively low blood phosphorus, leads to osteoporosis in adults, and rickets in children. Due to the poor absorption of phosphorus in sprue, the usual reciprocal relation between blood calcium and phosphorus does not obtain. In Hanes (4) experience, the bony changes in sprue are not as common in tropical climates as in non-tropical, because the increased activity of vitamin D from sunlight neutralizes in a measure the calcium deprivation. In view of the frequent association of tetany, it is interesting to note that Bennet, Hunter and Vaughn (20) found with the slit lamp incipient cataract in many of their cases of sprue. d. *Glucose tolerance curve.* The low glucose tolerance curve is the result of defective intestinal absorption. There is no defect in the utilization of glucose because once it is absorbed or given parenterally, the respiratory quotient is normal (11). Apparently sluggish intestinal mobility is a factor in the absorption of glucose. May and McCreary (27) found in patients with coeliac disease that there was an appreciable rise in blood glucose after giving mecholyl which increased the peristaltic activity. e. *Avitaminosis.* The poor absorptive power of the gastrointestinal tract is reflected in evidences of multiple vitamin deficiency in sprue. That vitamin A is poorly absorbed is attested by numerous observers (4, 26, 28, 17). Inasmuch as the primary defect in sprue is a vitamin B deficiency, tests to prove such a deficiency are not necessary. Scurvy has been occasionally reported in sprue, (15, 1, 4) and vitamin C has been found low in sprue (4). Kirk, Sauter and Hayward (29) found a deficiency of vitamin K in a case of sprue with a pronounced hemorrhagic tendency. f. *Hypoproteinemia.* Despite the fact that nitrogen excretion is only slightly above normal and that amino acids are well absorbed (4) a hypoproteinemia occurs due to both loss of protein and deficient intake and perhaps also to deficient formation, as in pernicious anemia. The hypoproteinemia is manifested in the frequency of

edema. In Snell's (1) series it occurred in 11 of 32 cases. In pancreatogenous steatorrhea there is always a profound loss of nitrogen in the stool (4, 11). g. *Gastrointestinal x-ray pattern in sprue.* Snell and Camp (30) first called attention to a characteristic x-ray pattern in sprue, consisting in delayed mobility and an alteration of the mucosal relief of the small intestine in that the contour is smooth; the valvulae conniventes are obliterated, the barium lies scattered and the colon is dilated. Golden (31) demonstrated the same pattern in pancreatogenous steatorrhea, in avitaminosis without steatorrhea and in pellagra. It is not seen in uncomplicated pernicious anemia. Apparently this pattern is conditioned by a number of factors. First, the diminished intestinal mobility; and second, the steatorrhea itself. Ravdin and his coworkers, (32) showed that in normal individuals the ingestion of olive oil causes an x-ray pattern resembling that found in sprue.

*Relation of sprue to pellagra.* Pellagra resembles sprue in a number of ways (3, 22, 1, 4, 15, 33, 34). In pellagra, stomatitis, glossitis, diarrhea and loss of weight and prostration are exceedingly common. Achlorhydria according to Sydenstricker (34) is present in most cases, even after histamine. While a hypochromic anemia is the rule, a hyperchromic (34) and megalocytic (35) anemia occurs in a small percentage of cases. Although skin lesions resembling pellagra are occasionally seen in sprue (1, 22, 3) they are not nearly as widespread, or as intense, nor do they lead to ulceration (4). Combined sclerosis is occasionally observed in pellagra (36). In both pellagra and sprue there is atrophy of the mucosa of the gastrointestinal tract. Furthermore, there is a striking parallelism in that both are deficiency diseases. In pellagra the deficiency is the vitamin B complex of which nicotinic acid and riboflavin are the dominating factors (P.P. factor). Sydenstricker has observed pellagra following a high carbohydrate diet in patients with diabetes mellitus who take large doses of insulin. Tbus far the intrinsic principle has not been found missing in pellagra (37, 34, 38). Sydenstricker in a fatal case of pellagra found the hematopoietic principle in the liver. Observations as to whether the intrinsic principle is always present in pellagra are still too few; at all events its presence, as determined thus far at least, probably accounts for the fact that the anemia in pellagra is of the hypochromic type. As in sprue, the acid in the stomach slowly returns after the administration of nicotinic acid; it may take 2 years (34). The similarity between the two diseases is further borne out by the experiments of Miller and Rhoades (2) who produced the syndrome of sprue in swine by giving the Goldberger diet, which is deficient in the P.P. factor, and which in dogs produces the black tongue disease, a malady closely allied to pellagra. Indeed, Harris and Harris (35) report and quote a number of cases of the transition of pellagra into sprue and ultimately with the blood picture of pernicious anemia. Strauss (39) quotes a large number of reported cases of gastrointestinal disorders that were followed by pellagra.

It is apparent that the pathologic physiology of the two diseases overlap to a considerable extent; and whether one or the other disease arises depends in all probability upon the nature of the deficiency, which may even be one that is

still undiscovered, or in a peculiar combination of deficiency principles. It is also by no means improbable that there may be a constitutional factor.

Many of the clinical features of the sprue syndrome are duplicated by other disorders in which the pathologic physiology again overlaps. We refer to pancreatic disease, and stricture and fistulae of the small intestine.

*Pancreatic disease.* Disease of the pancreas sufficient to completely inhibit the entrance of pancreatic juice into the intestine results in steatorrhea, with wasting, bulemia, diarrhea and a moderate degree of anemia. Snell (1) reports two cases of pancreatic lithiasis in which a macrocytic anemia and a gastrointestinal x-ray pattern like that of sprue was present. Experimentally, (40, 41) by complete exclusion of the pancreatic duct from the intestine or by the artificial production of a pancreatic fistula there is a loss of fat and carbohydrate in the feces and an increased excretion of fecal nitrogen which is related to the increased bulk of the feces. One gains the impression that the syndrome of complete pancreatic insufficiency has not been studied adequately from the clinical aspect. In children, on the other hand, this syndrome appears to have received greater attention, probably because it is more common. There is a malady, only recently described, known as fibrocystic disease of the pancreas, which mimics the sprue syndrome closely (42, 43). It is apparently a congenital and sometimes familial lesion; the symptoms arise in the earliest months of life and in its most common expression the malady is characterized by a failure to gain weight, diarrhea with large foul and fatty stools, infantilism, osteoporosis, usually a low glucose tolerance curve with occasional hypoglycemic symptoms, and a secondary anemia (42). There is a diminished absorption of vitamin A, apparently due to diminished intestinal mobility because it can be relieved by prostigmine (28) or by cascara or posterior pituitary extract (44). Fibrocystic disease of the pancreas can be distinguished from true coeliac disease by the finding of low or absent trypsin in the duodenal content. The determination of amylase and lipase is less reliable (45). Fibrocystic disease of the pancreas represents, in all probability, the majority of cases of "coeliac disease" in children that do not respond to treatment.

*Intestinal strictures and fistulas.* The occasional close simulation of the sprue syndrome by intestinal stricture was first described by Faber (46). The most complete summary of the subject is that of Barker and Hummel (47) who collected 51 cases including two of their own. The lesions are varied. The small intestine is principally involved, either by a tuberculous or non-tuberculous stricture; the large intestine, less frequently, by a stricture which may be either tuberculous or carcinomatous. Of 18 cases in which an anastomosis was found, the sprue syndrome followed an entero-enterostomy most frequently, less so gastro-colic fistulae or a gastro-jejuno-colic fistula. The clinical expression is characterized by diarrhea, glossitis, occasional icterus and less frequently evidences of cerebrospinal involvement. In 3 cases there was a combined sclerosis. Anemia was present in 100 per cent of all cases; in 39 of the 51 cases it was macrocytic and in 32 hyperchromic in type. An achlorhydria was found in 53 per cent. Of five cases which were tested with histamine, a true achlorhydria

was found in 4. The intrinsic principle was tested in 2 cases; it was present in one and absent in the other. In their own two cases, the excellent responses made by administering the extrinsic factor furnished indirect evidence that the intrinsic factor was present. The glucose tolerance curve was determined in 4 cases; in one it was flat, in the other 3 it was practically normal. The bone marrow resembled that of pernicious anemia. While many of the patients responded well to parenteral liver therapy, it obviously could not effect a cure. This was obtained in six cases when the continuity of the intestine was restored by operation. The precise mechanism whereby this syndrome arises in the course of these strictures and anastomoses of the intestine has not been demonstrated, but in all likelihood further investigations will probably show that the mechanism is similar to that which Castle and his coworkers (3) found in sprue, the difference being that in the latter the deficiency was the result of a prolonged lack of the extrinsic principle, while in the former, this principle is not absorbed.

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CHAPTER 20

# EMPHYSEMA

While emphysema has had adequate study, the conclusions lack not only unanimity but correlation, because the malady has been largely studied from the static rather than the biological viewpoint. It is interesting to note, as a corroboration of this thesis, that some active students of the disease have completely reversed their stand as the result of more prolonged observation.

*Varieties:* A large number of acute emphysemas are *compensatory* or perhaps better termed *complementary*, sequential to a greater or lesser involvement of thoracic space by pneumonia, atelectasis, pleural exudates, etc. These are transient and subside completely when the primary process has disappeared. On the other hand, if a considerable portion of the chest space has been compromised by a chronic process, for instance, tuberculosis, pulmonary fibrosis from excessive radiation, pneumoconiosis, non-malignant pulmonary or pleural neoplasms, extensive bronchiectasis, bilateral and extensive pleural adhesions, etc. a permanent emphysema develops which may lead to a hypertension of the pulmonary circuit, precisely comparable to that conventionally noted in the commoner obstructive variety of emphysema.

The emphysema that arises in prolonged mountain sickness may also be regarded as compensatory to the anoxemia (1). This has been reproduced in animals by prolonged exposure to low oxygen tensions (2).

There is a transient emphysema that occurs occasionally in children with pertussis, due, probably, to violent coughing and the excessive activity of the normal and accessory muscles of respiration which expand the chest wall (3).

Whether a chronic bronchitis may give rise to a permanent emphysema by the same mechanism seems very likely, if one may judge from the sequence of clinical events. An added factor may be the narrowing of the respiratory passages from the swelling of the mucosa. I have noted the development of emphysema on a number of occasions as the result of chronic cigarette cough. On the other hand, a chronic bronchitis often follows an emphysema, so that this common association may be both a cause and effect.

The *senile* variety of emphysema is regarded by most observers as a distinct type, secondary to senescent changes in the thoracic cage. Freund (4) ascribed the primary lesion to ossification of the costal cartilages. Kountz and Alexander

(5) believe the barrel chest results from a primary disease of the intervetebral disc which at first straightens the dorsal spine and later results in a kyphosis. Kerr and Lagen (6) described a form of emphysema occurring in the 5th and 6th decades that follows a postural syndrome due to obesity and a pendulous abdomen. Changes in the dorsal spine result with flaring of the ribs and the formation of a barrel chest. There is therefore evidence that a type of emphysema, senile if one may call it, that is secondary to disease of the bodily framework. In this sense, this type may also be regarded as compensatory. To be sure, Tendeloo (3), a persistent student of the disease, denies such a genesis, and holds that the primary change is a loss of pulmonary elasticity incident to age, and that the changes in the framework are subsidiary. This will be discussed later. In senile emphysema, the lungs are small and collapse when the thorax is opened in contrast to the obstructive type. Clinically, senile emphysema is fairly innocent during a larger part of its course. The oxygen saturation is normal and there is no retention of carbon dioxide; the diaphragm retains almost its normal excursion and breathing is largely abdominal. The heart remains normal in size, unless complicated by an associated hypertension or myocardial disease. Even in uncomplicated senile emphysema hypertension of the pulmonary circuit may follow. This eventuality is infrequent because the patient first succumbs to another senile disorder.

The most common variety is the *obstructive* type. This follows any disorder in which expiration is hindered, most frequently bronchial asthma, less frequently obstructive lesions of the bronchi due to neoplasms (usually adenoma), mediastinal tumors, aortic aneurysm, chronic bronchitis and obstructive lesions of the larynx. This type can be reproduced experimentally by obstructing the trachea with a brass tube containing a valvular attachment (7, 8). In obstructive emphysema, the lung is voluminous, and does not collapse when the chest is opened, due to loss of elasticity. The lobules are larger and often fuse together by rupture of the intervening septa (9). The terminal bronchioles are dilated, the lung is pale in the early phase due to extensive obliteration of capillaries.

*Microscopic pathology.* In obstructive emphysema this varies profoundly depending on the stage of the process. In the early stages, before any degree of hypertension of the pulmonary circuit has arisen, the alveoli are much distended, the walls are thin and many of the capillaries are obliterated. The elastic tissue is frayed and broken. When hypertension of the pulmonary circuit supervenes, dilatation of the remaining capillaries ensues with progressive productive changes in the walls of the alveoli, so that they become thickened, often with hyalinization. (10). The lung now presents the morphology of brown induration.

*Pathological physiology.* In obstructive emphysema the chest has the characteristic barrel shape, but this deformity is now secondary and not primary as in the senile and postural varieties. The diaphragm is pushed downward and its excursions are diminished. The chest is thus maintained in a greater or lesser inspiratory position. The heart often assumes the configuration of the "drop heart" in the earlier stages, before hypertension of the pulmonary circuit and heart failure have set in. Breathing is largely carried on by intercostal and

accessory muscles of respiration together with the abdominal; as a consequence these muscles and especially the abdominal often reveal a striking hypertrophy in obstructive emphysema. At the same time, intraabdominal pressure increases and it is presumed that, by pressure upon the abdominal veins, the return flow of blood to the heart is impeded. This may account in part at least for the relief patients derive from an abdominal belt which facilitates the venous return.

In the course of the maturation of the emphysema, a host of other factors participate.

a. *Loss of elasticity.* Henneman and Metz (11) measured the elasticity of segments of normal lungs and found a progressive increase up to the 20th year. After the 25th year there was a progressive decrease, which they and Tendeloo (3) regarded as provocative of the senile type. They also measured segments of lungs of the obstructive type and found a loss of elasticity greater than the age demanded. Christie (12) showed convincingly in the living subject, by simultaneous measurements of the intrapleural pressure and the tidal air, a profound to almost a complete loss of elasticity in obstructive emphysema. This loss of elasticity brings in its train important sequelae. Normal expiration which is largely a function of the pulmonary elasticity and is passive, is replaced by active muscular effort. Respiration is further impeded because the chest wall is already in the state of deep inspiration and the excursions of the diaphragm are small. In addition, Christie presents evidence that "the peripheral distended and relatively ischemic alveoli are over ventilated at the expense of the deeper and more normal alveoli. The subsequent diminution of the effective tidal air is responsible for some if not all of the anoxemia and $CO_2$ retention observed in emphysema." This explanation corresponds closely to that demonstrated by Haldane (13) many years ago. A further consequence of the loss of elasticity is the tolerance such patients evince to spontaneous and artifial pneumothorax.

b. *Changes in intrapleural pressure.* The progressive loss of pulmonary elasticity after the 20th year demonstrated by Henneman and Metz (11) are somewhat paralleled by the observations of Prinzmetal and Kountz (14) who found during the fourth decade both a reduction of vital capacity and in the ability of the individual to lower his intrapleural pressure. Kountz, Pearson and Koenig (15) found in emphysema that the intrapleural pressure was less negative than in normal individuals. This finding apparently represents a fixed stage of the identical change noted by Prinzmetal (2) during an asthmatic paroxysm, and affords another example of the transition from an exaggerated normal function to a fixation of that function, which we have termed "hyperkinesis" (16). Prinzmetal (2) demonstrated the same phenomenon in experimental bronchoconstriction.

c. *Venous pressure.* Kountz and his associates (8) found during an asthmatic attack and also in emphysema that the venous pressure rises more or less parallel to the rise in intrapleural pressure, due to interference with the venous return. That was also true in experimental emphysema. In asthma, the rise in venous pressure promptly returns to normal after the attack, but when emphysema is associated, the pressure dropped slowly, sometimes in the course of days. These

rises in venous pressure only exceptionally attain heights above the normal range in emphysema uncomplicated by heart failure, which is in accord with the findings of Weiss and Blumgart (17) who found the venous pressure normal in emphysema, except in "severe" instances. However, if patients with emphysema are followed over a sufficient span of time, a progressive rise in venous pressure is often noted pari passu with clinical evidences of an increase in intrapulmonary arterial pressure, such as increasing cyanosis, breathlessness and an increasing density of the pulmonary markings. Inasmuch as the transition from hypertension of the pulmonary circuit to right heart failure is a gradual one and inasmuch as normal venous pressure represents a range rather than a precise mathematical quantity, it is difficult to determine when, in emphysema, the rise in venous pressure determines the induction of heart failure. In time the venous pressure attains a height that definitely spells failure of the right heart. The venous pressure is one of the factors that determines the difference between mild and "severe" emphysema. The time element affords an explanation, in part at least, for the diverse venous pressures reported by different observers in emphysema. Obviously we are referring only to uncomplicated cases of obstructive emphysema. When a cardiac lesion is associated, an elevated venous pressure may arise through that agency alone.

d. *Circulation time.* Here as well, static measurements of the circulation time in emphysema have led to diverse interpretations. These afford at best only linear relationships. Weiss and Blumgart (17) in 33 patients with obstructive emphysema found the circulation time with the radium method normal in 29 and only moderately elevated in four. Indeed in some patients the circulation time was faster than normal. Even in severe cases, the circulation time was less then that witnessed in myocardial failure. These observations demonstrate "that even severe chronic emphysema does not necessarily obstruct the blood flow sufficiently to interfere with the normal velocity of blood flow through the lungs". They regard this increased velocity as an attempt to compensate for the insufficient ventilation. Tarr, Oppenheimer and Sager (18) in 19 patients using decholin found the circulation time normal in 13. In the remaining 6 it was prolonged up to 22 seconds. It is natural to infer that when a prolonged circulation time is found in emphysema that heart failure has set in. Indeed of the 6 cases of Tarr, Oppenheimer and Sager, four revealed clinical evidences of congestive failure, while in two it was absent. In any event, the mere circumstance that the circulation time in emphysema is sometimes normal and sometimes prolonged indicates that there must have been a transition period, but when heart failure entered cannot be determined by the circulation time alone, without taking other clinical data into consideration. In other words, a progressive rise in circulation time in emphysema indicates changes in dynamics that lead to heart failure but does not necessarily imply it.

The impression must not be gained that these abnormal functions that arise in the course of an obstructive emphysema can be divorced from each other. Not only is there a greater or lesser interplay but the precedence has not always been established. Above all, the time factor must always be introduced. The

summation of these abnormally acting forces in emphysema have profound effects upon the organism.

1. *Ventilation.* The vital capacity is consistenly reduced, although the total capacity is not changed. There is an increase in the residual air at the expense of the complemental and supplemental air (19). Hurtado and his coworkers (20) find that the ratio between the residual air and the total capacity affords a close correlation with the degree of respiratory disability, and is therefore useful in emphysema for diagnostic and prognostic purposes.

2. *Anoxemia.* In 24 cases of pulmonary emphysema Hurtado et al (20) found the oxygen saturation to vary between 72.9 and 97.7 per cent with a mean value of 88.2 per cent, a value definitely less than normal. In 20 cases it was below the normal limit, 94 per cent, and in 14 the saturation was less than 90 per cent. Meakins and Davies (21) found the saturation of arterial blood varied from 86 per cent to 90 per cent. Lemon's (22) average was about the same and varied between 84 and 89 per cent. Himwich and Loebel (23) reported the arterial oxygen saturation in three emphysematous patients. In two it was normal. In the third it averaged around 83 per cent; with slight exercise it sank to 23 per cent one to two minutes later. The comparatively wide range of arterial oxygen saturation again leads one to believe that there is a progressive loss with time and the intensity of the process.

The anoxemia is usually of sufficient degree to produce the characteristic cyanosis. Lemon (22) calculated that the degree of unsaturation of the capillary blood attains that formulated by Lunsgaard and van Slyke as necessary to produce cyanosis. Inasmuch as prolonged anoxemia as in mitral disease and mountain sickness, gives rise to such compensatory phenomena as polycythemia, increased size of red blood cells and increased corpuscular and blood volume, one would expect similar changes in emphysema. Reported observation of such compensatory changes are rather conflicting. Some observers report findings within the range of normal, others abnormal. Under any circumstances, the ranges are wide. These discordant results are in part due to different methods employed, but there can be little question that they are largely due to the fact that the time element is missing. Repeated measurements at prolonged intervals in the same individual would be far more illuminating. It is a well attested clinical observation that in longstanding cases of emphysema, marked polycythemia is usually marked and in some cases even an increase in blood volume has been noted (24). Many so-called "black cardiacs" are emphysematics. Arriliga (25) and Escudero (26) have reported a number of such under the false classification of "Ayerza's disease".

3. All observers agree that there is a *retention of* $CO_2$ in the blood in emphysema. Christie (12) presents evidence which leads him to believe that as a result of the loss of pulmonary elasticity the peripheral distended and relatively ischemic alveoli are overventilated at the expense of the deeper and more normal alveoli. The subsequent diminution of the effective tidal air is held responsible for some if not all, of the anoxemia and $CO_2$ retention. Scott (27) long before this showed that there was $CO_2$ retention in emphysema. He also showed that the blood bicarbonate was elevated, thus maintaining the hydrogen ion concen-

tration within normal limits. He also showed that patients with emphysema have an increased tolerance for rebreathing with relatively high percentages (8 to 10 per cent) of $CO_2$ for 10 to 15 minutes, showing relatively little increase in minute volume and evincing no subjective symptoms of distress. Slightly higher percentages of $CO_2$ cause acute distress. These observations have been confirmed.

*Effect of emphysema on the heart.* Although in the past doubt has been expressed in some quarters as to whether emphysema affects the heart, all are now agreed that it does, and that the primary mechanism is hypertension of the pulmonary circulation. There is no clinical method of measuring the pressure in the lesser circulation[1] but the accentuation of the second pulmonic sound in uncomplicated emphysema indicates its presence.

There are a number of possible peripheral resistances that may contribute to the development of hypertension of the pulmonary circuit: a. the diminution of the capillary bed due partly to atrophy of the walls of the alveoli and partly to actual desruction by rupture of many of the alveolar septa. The pale color of emphysematous lungs in the early phases is the expression of these factors. b. the expansion of the alveoli causes a compression and stretching of the interalveolar arterioles (28). c. Fishberg (24) suggests that the chronic cough raises the intraalveolar pressure to such an extent as to compress the minute vessels of the lungs; the hypertrophy of the right heart occasionally observed in pertussis may be accounted for by the same mechanics. d. it is possible that the less negative intrapleural pressure may compress the thin walled pulmonary veins sufficiently to cause a rise in pulmonary arterial pressure.

A sustained rise in intraarterial pulmonary pressure leads inevitably to hypertrophy of the right ventricle. Kirsch (29) found in emphysema that the dilatation and later hypertrophy first affected the outflow tract, a process precisely comparable to that observed in the left ventricle in hypertension of the greater circuit. This was confirmed by Parkinson and Hoyle (30) radiographically and checked by post-mortem observations. They found a prominent conus which in part represents the outflow tract, in 33 of 90 cases of emphysema. In later stages the body of the right ventricle enlarges due to enlargement and dilatation of the inflow tract.

Coincidentally, dilatation of the pulmonary artery occurs. This is apparent during life roentgenologically by the increased width of the pulmonary artery at the hilus and by the enlarged conus. In later stages, when the dilatation becomes extreme, dancing pulsating shadows may be seen. At post-mortem, dilatation of the entire pulmonary tree always accompanies gross arteriosclerosis of the pulmonary vessels, the hall mark of hypertension of the pulmonary circuit.

Clinically enlargement of the right heart in the early stages of emphysema may not be susceptible of proof because the low diaphragm causes the heart not only to drop but to rotate so that the transverse diameter is not appreciably widened.

[1] Recently Cournand has been able to measure the pressure in the right auricle by introducing a catheter by way of the brachial veins. It seems to be a harmless procedure and has already contributed much to our knowledge of the dynamics within the pulmonary circuit.

*Pulmonary arteriosclerosis.* We have previously expressed the view (10) (see Chapt. 3) that arteriosclerosis is a process that begins at birth, characterized essentially by a progressive splitting and hyperplasia of the elastica and of the intima, and that these changes represent an adaptation to the progressive rise in intravascular pressure that proceeds from birth to maturity. When hypertension occurs, the process comes earlier and is accelerated and intensified. The pulmonary artery also partakes in this process (31) but inasmuch as the pressure within this vessel is low (only one-sixth that in the aorta) the pulmonary artery is singularly free from gross changes of arteriosclerosis as compared to the vessels of the greater circulation. For this reason there is a remarkable difference in incidence of gross arteriosclerosis between the two circulations. When however, hypertension of the pulmonary circuit arises, the normal hyperplastic process is intensified, and gross arteriosclerosis becomes manifest. With the exception of rare instances in senile individuals, gross arteriosclerosis of the pulmonary artery never occurs unless a lesion that might dynamically cause a hypertension of the pulmonary circuit is present (31). Pulmonary arteriosclerosis is therefore, as we previously stated, the hall mark of hypertension within this vessel. We have not observed an emphysema of any degree or duration that did not reveal gross arteriosclerosis of the pulmonary artery. That emphysema is a common cause of pulmonary arteriosclerosis is shown by the fact that in 62 such instances, emphysema was found in 12, a percentage of 19.3 per cent. The hypertension in the pulmonary circuit in emphysema is reflected not only in the arteriosclerosis within the pulmonary artery but also in sclerotic changes in the endocardium. In uncomplicated emphysema the endocardium of the right ventricle and to a lesser extent of the right auricle show thickening. The endocardium of the left side of the heart is intact, in contrast to uncomplicated hypertension of the greater circulation when the endocardium of the left side of the heart shows thickening. Eventually the increased pressure in the pulmonary circuit is reflected forward into the pulmonary capillaries. These dilate giving rise to a beaded appearance of the alveolar wall and the alveolar lumen becomes narrowed, which accounts for some of the loss of vital capacity. The dilatation of the capillaries is always accompanied by a fibrous thickening of the capillary wall which in places becomes hyalinized. One may regard the entire process as an arteriocapillary fibrosis, precisely comparable to that which occurs in the greater circulation in hypertensive disease. Under such circumstances, the emphysematous lung changes its physical characters; it becomes carneous, firm and congested. Some years ago I (32) described such a lung in a patient in whom over a period of many years, I had observed the transition from pure bronchial asthma to emphysema, and finally to right sided cardiac failure.

It must be insisted upon that the clinical phenomena associated with emphysema are not the direct result of the arteriosclerosis of the pulmonary arteries as some aver, but the result of the altered dynamic forces that evoked it.

The increased amplitude of contraction consequent upon the hypertrophy of the right ventricle compensates for the increased pulmonary resistance for a great or lesser period, often for years. Eventually, unless an intercurrent complication arises, the compensation no longer suffices and dilatation of the inflow tract of the right ventricle ensues. This is evidenced roentgenologically

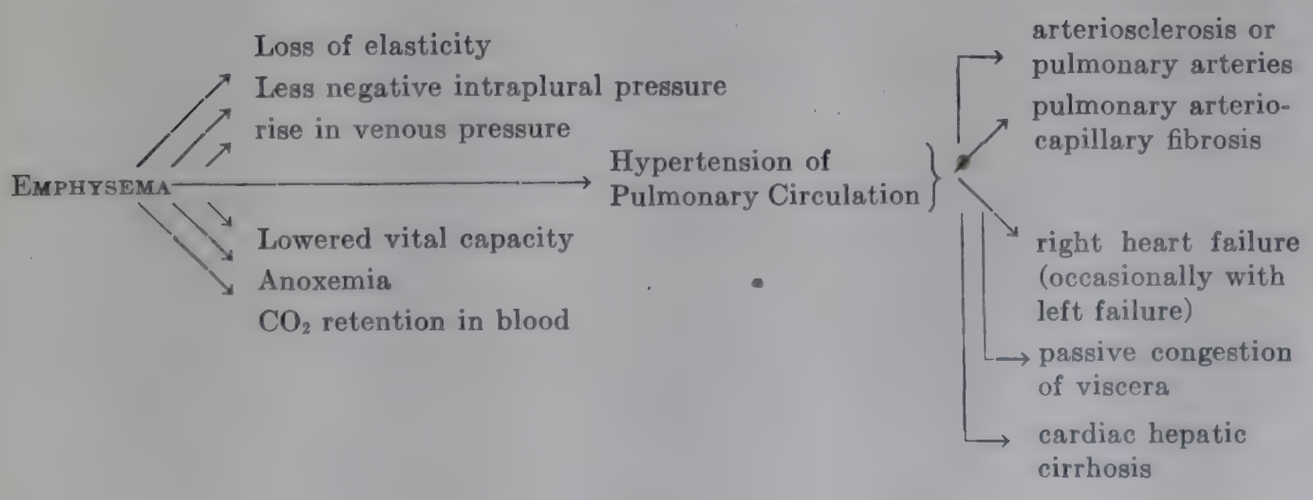
by an an increase in the size of the right ventricle. This dilatation in turn forces the right auricle to empty against a positive pressure and an appreciable rise in venous pressure results. The increased pressure within the right auricle extends downward through the inferior vena cava into the hepatic veins and thence into the liver which enlarges and becomes nutmeg in appearance. This entire system dilates and forms a reservoir which acts temporarily as a dam against the steadily mounting venous pressure. In time cardiac cirrhosis arises which is always associated with sclerosis of the hepatic veins (33). The morphological changes in the liver represent pathogenetically a venocapillary fibrosis, comparable to that which occurs in the lung, the hepatic vein taking the place of the pulmonary artery. These processes within the liver are not peculiar to emphysema but follow any prolonged hypertension of the pulmonary circuit from any cause (see Chapt. 1).

A rise of venous pressure well beyond the normal range is therefore one of the earliest manifestations of beginning failure of the right heart. Death often occurs from pure failure of the right heart with the classical picture of intense cyanosis, breathlessness, low grade renal insufficiency and anasarca. The entire series of events conforms to the typical clinical picture of "cor pulmonale", a common sequence of obstructive emphysema. Of 48 cases of "cor pulmonale" observed by Scott and Garvin (34) 46 were associated with emphysema. In 32, emphysema was the sole cause; in the remainder the emphysema was associated with silicosis or tuberculosis.

Occasionally in emphysema involvement of the left ventricle follows. There are a number of possible explanations. 1. According to Starling and his coworkers (35) a sustained and progressive rise of effective venous pressure causes an increased stroke volume in the left ventricle. This inevitably leads to hypertrophy and eventually to dilatation. 2. The anoxemia must augment the work of the left ventricular muscle that is already overburdened by an increased venous return. Such a heart requires more oxygen than normal but the amount falls short owing to reduction in coronary flow that accompanies dilatation of the heart (36, 37).

More often, left ventricular enlargement in emphysema is the result of an associated hypertension or coronory disease, since these maladies have the same age incidence.

BIOLOGY OF EMPHYSEMA



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CHAPTER 21

# PSYCHOSOMATIC MEDICINE

Psychosomatic medicine is nothing new; it is as old as Hippocrates. Its recent interest represents more a crystallization of centuries of thoughts than the discovery of new mechanisms of disease processes. The reason why its renaissance has been so long delayed can be largely attributed to the teaching of mechanized methods of medicine in our colleges, traceable directly to the dominance of the Continental school in the past century which taught and still teaches that disturbances of function, which we call disease, always follow morbid tissue changes. But it is slowly but surely dawning upon us that the reverse is sometimes true and that morphological changes may be the result of disturbances of function which are largely conditioned by emotional factors, and that therefore morbid anatomy, chemical and humoral changes may sometimes be the results and not always the cause of disease. Curiously, this modern trend represents a reversal to the doctrine that Hippocrates taught, that a disease and the temperament cannot be divorced. It is satisfying to know that in recent decades there has been a decided trend in these habits of thought in our medical schools, and that psychiatry, not limited merely to the study of insanity, is receiving a larger share in the medical curriculum. This may be the reason why the study of psychosomatic medicine is largely within the hands of the youth of our profession.

What is a psychosomatic disease? It is not easy to define because we do not know where the "psyche" ends and the "soma" begins. Tentatively we may define a psychosomatic disease as one in which purely psychogenetic factors result in organic disease. Although organic disease has thus far not been discovered in the psychoses by methods at our command I would include them in the psychosomatic diseases because biologically they behave identically. There is no doubt that such changes exist in the psychoses, as proven by the recovery that occasionally results by physical or chemical means. As a matter of fact, the distinction between functional and organic, a concept that psychiatrists have viewed as inviolable for centuries, has been rudely jarred by the discovery that physico-chemical agents may profoundly modify abnormal behavior, and that the electroencephalogram may record what had hitherto been regarded as purely mental processes. The implications are enormous not only for a clearer approach

to the study of mental processes but also for wider avenues for therapy. Freud (1) even in 1928 had an inkling of such an eventuality when he wrote "Because of the essential unity of the two things that we divide into somatic and psychic, one may prophesy that the day will come when the avenue from biology and chemistry to the phenomenon of neurosis will be open for our understanding and we hope also for therapy." The schism between vitalism and materialism is slowly breaking up. One may compare the psychiatry of today with chemistry and physics a century ago before the atomic theory. One may foster the wild hope that some day another Dalton and perhaps another Thomson may discover units of human behavior like the atom and the electron so that they may be interpreted in terms of physico-chemical reactions rather than as vitalistic processes.

Students of psychosomatic disease in their enthusiasm have lately included within this domain the effect of emotion on individuals with previously existing organic disease, for instance the excitation of pain by emotion in coronary disease. Nor may one include a reversal of the process; the study of the effect of somatic disease on the psyche; what one calls somatopsychic medicine. This is a fascinating and largely untouched field. In this sense, all medicine is psychosomatic or somatopsychic.

The definition we have given implies that physiological changes merge imperceptibly into organic disease. Heretofore, the terms "functional" and "organic" have been sharply dichotomized, because in the first, structural alterations are not found, while in the latter they are. What we really mean is that *thus far*, no structural changes have been found within the scope of our present resources. It is impossible to conceive of an abnormal physiologic change, a contraction of or dilation of a vessel or gut, an increase in gastric secretion, abnormal sweating, as instances, without some simultaneous tissue change. The difference between a functional change and an organic one is in reality a quantitative and not a qualitative one, and when one passes into the other is determined only by the limitation of our senses. That emotions may cause profound physiological changes that are even measurable, requires no argument. You are all familiar with Cannon's (2) concept of homeostasis in which these responses are viewed as defense mechanisms against pain, hunger, fear and rage. The term "emotion" is generic and includes many varieties. It certainly is not synonymous with "worry" an expression, unfortunately, that physicians who are not psychiatrically minded, use to describe every variety of emotion, and has even insinuated itself in some recent psychosomatic literature. Emotion may be fear, anger, distrust, anxiety, hate, rage, love, sorrow, joy, and the physiological response varies with the variety of emotion. Witness the blanching of the skin under the stimulus of fear, and the [illegible]shing that comes with joy, the suppression of sweating that comes with fear [illegible] increase with aggression or vice versa. Wolff and Wolf (3) made some inte[illegible]g observations on their famous Tom, their laboratory helper, who for 47 years fed himself through a gastrostomy opening, made for atresia of the esophagus after swallowing hot clam chowder. When an episode arose that

created fear in Tom or what Wolff and Wolf call an "alarm" reaction, the secretion of gastric juice ceased. On another occasion, when Tom felt aggression, the secretion increased to triple the normal. Hoelzel (4) recently reported interesting observations on his own gastric secretion. For reasons of his own he was in the habit of testing the acidity of his gastric secretion daily. Suddenly he received a threat that he might be shot, and during this episode his gastric secretion rose to appreciable heights; when the threat was abolished, the secretion returned to normal. Pavlov's experiments on the variety of reactions from different conditioning reflexes in dogs, contributes further illustrations. Unfortunately, in man, experiments on the excitation of a wide range of functions by different kinds of emotion are not feasible. Above all, it is not only the variety of emotion but the way in which "these emotions are experienced" as Stanley Cobb puts it, that determine the physiological response. Much of the current thinking on psychosomatic problems loses significance unless this is grasped. One individual trembles, the second vomits, the third gets palpitation, the fourth gets increased peristalsis, the fifth flushes, the sixth pants for breath, the seventh feels a lump in his stomach, and these symptoms are reflected in physical expressions such as changes in blood pressure, increase or suppression in gastric secretion, increase in blood sugar, increase in intestinal secretion and tachycardia. I am confident that if such individuals could be promptly x-rayed, they would also show spasm of the cardiac sphincter and pylorus and hyperperistalsis of the gastrointestinal tract. The internal secretions are probably profoundly affected by emotions, but proof by other than clinical observation is as yet unconvincing. Nor has any graphic precise evidence been submitted to prove that disordered functions become fixed under protracted emotional states, nor can one, for the present at least, visualize a method that will afford such evidence either in the human being or experimentally. Psychiatric problems unfortunately do not lend themselves, except in very limited circumstances, as in the case of Tom, to laboratory proof. The only way whereby we can surmise that such a fixation may take place is by noting the sequence of events by direct and prolonged clinical observation in the same individual. Happily, there are enough of these observations to make an impressive showing. Such observation is more within the scope of the general practitioner than of the consultant because the latter only sees a small cross section of the life cycle of the disease, and for the same reason, such studies cannot be made in hospitals, for here only one observes the terminal phases of disease.

It is therefore not only the variety of emotion, but the individuals' reaction to the emotion that are significant in the mechanism that leads to pychosomatic disease.

Sceptics reason thus: many persons, especially in these days of social and economic insecurity, are subject to severe emotional reactions, but only a few acquire psychosomatic disease. These critics have failed to grasp the fact that it is not the reaction itself, but the impact of this reaction on a particular kind of individual that not only conditions psychosomatic disease but also the variety that will

eventually manifest itself. In this respect, psychosomatic disorders may be aptly compared to deficiency disease or to infections. Duality in causation runs like a thread throughout medicine. It is not the bacterium, but the impact of the bacterium in a susceptible individual that makes him sick, and even in disorders that are not infectious we are beginning to think again in terms of constitution. To regard constitution as comprising only physical attributes is a narrow viewpoint. Pragmatically, especially in respect to the study of susceptibility to psychosomatic disease, one must evoke a broader concept of constitution. A constitution may be physical, it may be psychological, usually it is both. There is argument as to how much of the constitution is hereditary or genotypic, and to what extent it is the result of environmental or phenotypic factors. When the physical makeup is part and parcel of the constitution, there is evidence that this is hereditary. For example, the sthenic habitus that is frequently found in hypertensive families, the anthropomorphic characteristics that Draper has described in patients with peptic ulcer, are largely genetic in origin. There is also no doubt that sometimes the psyche is largely hereditary; the frequent hereditary nature of manic depressive psychosis and paranoia is a proof. However, evidence thus far does not permit us to say to what extent the complex of characteristics which we call personality is genetic or environmental. It would lead us too far afield to enter into this much belabored subject. In recent psychosomatic literature there is repetitious argument that because a malady is often familial that it is hereditary. No one can study personality traits in families without being impressed that the tone and life outlook of the family are profoundly influenced not only by the attitude of the parents, but by the reaction of the siblings toward each other, either by direct imitation or by compensatory reactions. The evidence derived from psychoanalytic techniques indicates strongly that personality and the resultant behavior are conditioned by influences that begin at birth. Observations on the development of personality in identical twins brought up under different surroundings are confirmatory. Unfortunately there are altogether too few observations on the occurrence of psychosomatic diseases in identical twins. In the only case I have been able to find reported by Friedman and Kassanin (5) hypertension occurred in one and not in the other. The twin brothers were entirely opposite temperaments.

The difficulty in classifying types of personality is obvious to everyone who is cognizant of the wide variety of classifications that have been devised. Kretschmar divides them into the pyknic, athletic and asthenic types. There are the introverts and the extraverts, and Jung has subdivided these into the thinking, feeling, sensuous and intuitive varieties. Freud has introduced the adjectives, narcissistic, obsessive, schizoid and hysterical. The terms represent dominant traits and in the hands of their sponsors have proved useful as a working guide for the classifications of the neuroses. Unfortunately, people are not just one thing or another like flowers or plants, but are aggregates of many qualities modified by their interreactions so that there is nearly always more or less overlapping. Nevertheless, despite the difficulties in classifying, many students in psychosomatic medicine are active in synthesizing broad personality types in

which particular psychosomatic diseases are more likely to occur than in others. Unfortunately, thus far in only a few of the psychosomatic diseases have these studies been attended with any measure of success. Thus in Graves' syndrome in which the type personality is more clear cut than in any other psychosomatic disease, the individual is of the sensitive emotional type, unstable, with manic-depressive trends. Usually, one can trace the sensitivity to parental overprotection in childhood, resulting very frequently in parental fixations. This accounts for the greater frequency of Graves' disease in females, since they are more subject not only to parental but to social overprotection. I have applied the term "allergic to life" to the life pattern of these individuals. It is obvious that such folk will react deeply to either sudden powerful insults or to reiterated smaller ones; under such circumstances, the Graves' syndrome sometimes arises either suddenly or insidiously. One sometimes hears of apathetic Graves' syndrome. If one digs deeper, this apathy is found to be only a mask. In other words, Graves' syndrome represents the resultant of the impact of environmental factors upon a constitutional background. Of the vast number of physiological reactions set forth by the impact of these two factors and of the biology of the psychosomatic diseases, I shall speak later. In sufferers with peptic ulcer, the dominant personality trait is a strong aggression. They are born fighters with strong sadistic and masochistic trends. As would be expected such individuals are usually intolerant; indeed they are all or nothing folk and strong and lasting haters. We all hate at some time or other in our lives; but most of us express our hate outwardly. Some of us do it with our fists, some by calling names and others by pity, but because of their repressions, ulcer people dam up their emotions and literally consume themselves with anger.

As in Graves' syndrome, one finds frequently that the symptoms were initiated by a psychological trauma, the illness or death or a dear relative, economic distress, marital maladjustment, etc. This factor has a strong bearing upon the high incidence of peptic ulcer in the allied armies, due to the inability of many recruits to adjust themselves to military life. If one may judge by the clinical sequence of events, this impact of environmental factors upon a type personality sometimes both initiates and activates a preexisting ulcer.

In non-specific ulcerative colitis on the other hand, the dominant personal characteristic is a spirit of defeatism. Such patients are mostly dependent folk, indecisive and self-pitying. Their sense of guilt is expressed outwardly; usually it is against an individual and not against a situation. I shall leave the symbolic interpretation of the diarrhea to the Freudians. I have never met a patient with non-specific ulcerative colitis who was what one may call successful in life. Individuals with peptic ulcer and essential hypertension are often successful; the victims of Graves' syndrome sometimes are, usually in the arts, literature, painting, music, etc. A neurosis is sometimes a useful commodity. In individuals with non-specific ulcerative colitis patient and persistent questioning can usually elicit a psychological trauma preceding the onset of the symptoms and as in peptic ulcer, this trauma may initiate as well as activate a colitis.

In essential hypertension the positive characteristics of the patient are not easy

to define. Such a patient may best be described as the antithesis to the child in mental makeup. He does not play; he has no make believe. He lives a crowded and compact existence. There is no doubt that these traits are largely the result of insecurity, and so, unlike a child, he lives in the future and not in the immediate present. He doesn't play because this may divert his strivings to acquire future security. As a consequence, his mental range is usually narrow, but within this range it is terribly intense. In individuals with essential hypertension one cannot as a rule elicit a history of its having arisen after a sudden psychological trauma. Their whole aspect of life may be regarded as a psychological trauma, and for this reason hypertension is nearly always insidious in onset and slow in development.

Obviously all cases of essential hypertension are not psychogenic in origin. Some are due to obesity, to Cushing's disease, to pheochromocytoma, to lead poisoning and some, although rarely, to unilateral renal diseases. Psychiatrists often overlook this fact.

The personality patterns of other maladies, conventionally regarded as of psychosomatic origin, such as cardiospasm, mucous colitis, anorexia nervosa, neurodermatitis, and possibly certain cases of glaucoma have not yet been sufficiently elucidated. In manic depressive psychosis, the individual always revealed a wide range between elation and depression in his emotional reactions long before the psychosis became manifest. In paranoia, the person was always suspicious, eccentric and afflicted with profound obsessions. Those who are better qualified in psychiatry than I, tell me that these traits date back to childhood.

It may be that in the future these psychological patterns in psychosomatic disease will be more clearly demarcated by finer methods of approach; for instance, by the different disciplines of psychoanalysis. Thus far, however, the largest contribution the Freudian psychoanalysts have made to the study of psychosomatic disease has been in the unraveling of psychological mechanisms whereby these types of personality have developed. Occasionally a successful therapeusis has been obtained. Their efforts have unquestionably been valuable, but if I may be bold enough to venture a criticism, I would say that they would contribute more to the study of psychosomatic diseases by devoting more effort to direct clinical observation than by exercises in semantics and symbolism.

The overlapping of many of the components of these patterns helps to explain the not uncommon association of two or more psychosomatic diseases in the same individual. Essential hypertension and peptic ulcer, hypertension and Graves' syndrome, Graves' syndrome and peptic ulcer, manic depressive psychoses with Graves' syndrome, peptic ulcer and paranoia are not infrequently associated. The combinations are numerous. Curiously, peptic ulcer and non-specific ulcerative colitis rarely are associated. The reason probably is that the two personality patterns are more or less antagonistic.

Only a rabid psychosomaticist would insist that the impact of a persistent emotional situation upon a certain temperament is the whole story in the creation of such diseases. Most of us can think of individuals who conform to one of these types and who have not acquired their own particular psychosomatic disease.

Obviously, there must be other mechanisms that we are as yet unaware of, chemical, physical, endocrine, humoral, etc. We must also consider that psychosomatic diseases possess a long life cycle and that the incubation period may be one of many years. It has been my privilege to have witnessed this transition. Moreover, the powers of adjustment to emotional stress are not always constant. Compensatory mechanisms are always around the corner. One of the largest problems in psychosomatic medicine is the bridging of the wide chasm between the psyche and the soma. Clinically, if we are lucky, we can sometimes observe transitions in some of these psychosomatic disorders. For example, witness the catastrophic clinical changes between essential hypertension and the terminal cardiovascular disease. In Graves' syndrome, one can often note the transition from the larval phase, call it autonomic imbalance, Basedowid, formes frûstes, neurocirculatory asthenia or what you will, to the fully blown form with the classical quadrad of signs and symptoms. Although the earliest phase of peptic ulcer is in all probability gastric hypersecretion, we are at present unable to witness transition to ulcer formation, because with the diagnostic methods at our command, the presence of the ulcer can only be determined after it has fully developed. The observation of the intervening phase may come through serial gastroscopy. However, the experimental creation of a peptic ulcer, especially by the method of Mann and Williamson (6) affords a clue as to what we may expect to find in the human being. In non-specific ulcerative colitis we are entirely ignorant of the earliest phases. It would be intriguing if the earliest phase were mucous colitis but clinical facts are as yet insufficient to warrant such a statement. But there are a number of observations that lead us to believe that the larval form is an irritable or spastic colon. The initial phases of the other psychosomatic diseases that we have mentioned appear to be only mild expressions of the mature types and they have not been endowed in the past with a different nosological status.

The psychosomatic diseases thus lend themselves especially to study from the biological rather than the static viewpoint, an aspect that is missing in much of the current psychosomatic literature. It is to be regretted that much of the activity in psychosomatic medicine is mostly in the hands of pure psychiatrists. The converse is equally true; greater progress would come if the clinician were a better psychiatrist. In fact, many are not even receptive to the ideas underlying psychosomatic medicine.

Even if we knew more completely the clinical biology of these disorders, we would still be far from understanding the nature of the abnormal physiological responses kindled by their impact, their sequences, their interrelations and especially the manner whereby these physiological responses are converted into gross morphological changes. A vast host of mechanisms are set into play. There can be little doubt that many of the physiological changes are mediated through the autonomic nervous system and the hypothalamus, and the experimental work on stimulation or the abolishing of the activity of these centres has enlarged our knowledge appreciably. Cannon's work, especially, has far reaching implications, and he has emphasized the teleological or emergency nature of these reactions. Unfortunately, our methods of approach are still

crude and the interrelation between the autonomic, the somatic nervous system and the endocrine organisms are so close and so complex that it is difficult to isolate the reactions between the various systems. Unfortunately, the autonomic nervous system has been the victim of infinitely more speculation than of experiment. The autonomic nervous system is continually invoked as the "cause" of this or that psychosomatic disease. This has made sterile much of the work on the etiology of the psychosomatic diseases. The autonomic nervous system may be the mechanism whereby the physiological responses are mediated, and this, of course, is well worth knowing, but the determination of such a mechanism is by no means synonymous with "cause." Causality in disease constitutes a chain of circumstances and events and is never a single and isolated factor.

One can now grasp why the average conventional hospital history of a psychosomatic disease is woefully incomplete. Such histories only begin when the clinical manifestations have become apparent. But the malady began long before, sometimes even from birth. An adequate history of psychosomatic disease should therefore include a panoramic survey of the patient's entire life history, his reactions to the members of his family, his social and economic status, his loves, his fears, his strivings, his hates. Such tridimensional histories need not necessarily be recounted in psychanalytic detail; in most instances, gross data and not the microscopic details usually suffice. In view of the prevailing increase in the psychosomatic diseases, not to speak of the neuroses, the hospital of the future will be manned by a much larger body of psychiatrists than at present. A better solution would be to convert internists into psychiatrists.

Experimental investigations are handicapped by the fact that psychosomatic diseases are essentially human diseases; experimental methods to reproduce them have therefore largely failed because they cannot introduce the human equation. The only psychosomatic disease which has been successfully reproduced experimentally is peptic ulcer and this only by methods that are totally unphysiological for man. By the same token, lower animals are practically immune from the psychosomatic diseases.

Curiously, in all but one of the psychosomatic disorders there is a common variety of physiological response, namely an exaggeration of one or more normal functions. In essential hypertension it is the intravascular pressure; in Graves' syndrome the basal metabolic rate; in peptic ulcer, the gastric secretion; in ulcerative colitis, the tonicity, peristalsis and the intestinal secretions; in cardiospasm, the tonicity of the cardiac sphincter. This exaggeration applies as well to some of the psychoses; in manic depressive insanity, there is an exaggeration of the normal emotional rhythm between elation and depression. In paranoia, there is exaggeration of the normal affective state of mind. This concept may apply to certain forms of schizophrenia, but I am not sure. This exaggeration of one function is the dominant evidence of the disease, although an exaggeration of other normal functions in varying degrees of activity may partake in the clinical expression. I have employed the term hyperkinesis (7) to this process. One may construct the following biological sequence. Constitution + psychological trauma → hyperkinesis → somatic disease.

The only psychosomatic disease in which exaggeration does not apply is

anorexia nervosa. This malady is characterized by a depression of a wide range of functions; the basal metabolic rate, the body temperature, the estrogenic function, the blood pressure and the gastrointestinal muscular activity and its secretions. Why this psychosomatic malady should behave contrariwise to the other psychosomatic diseases is a mystery.

The hyperkinesis or hypokinesis in all these aforementioned disorders indicates that the search for a specific test will probably fail, because the transition from the normal or static phase to the abnormal or dynamic phase is subtle and the line of demarcation is an indefinite one. All bodily functions have ranges within a normal, not an exact mathematical quantity. The diagnosis of these diseases, therefore, depends upon a perspective of the composite picture in which a study of the personality and life history of the individual is a vital consideration.

Why does one person get hypertension, the second peptic ulcer, the third Graves' disease and so on? This is one of the important issues in psychosomatic medicine. The easiest solution would be to invoke the doctrine of "organ inferiority." This is purely hypothetical and I know of no evidence that justifies such a doctrine. The answer probably lies in the manner in which the individual reacts to emotion. I have already mentioned that one person vomits, the second trembles, the third moves his bowels, the fourth gets palpitation, the fifth flushes, the sixth feels a lump in the pit of his stomach, the seventh acquires a rise in blood pressure, etc. Usually, two or more of these reactions arise simultaneously. It is not difficult to conceive that these reactions which represent exaggerations of normal function may become fixed, provided the emotion is powerful enough and is experienced over a prolonged period. Alfred Cohn (8) reported an interesting observation in World War I. During his inspection of base hospitals in the week after the armistice, he found only rare instances of neurocirculatory asthenia, whereas previously they had been common. That this concept has some validity is reflected in some psychosomatic diseases in which clinical transitions may be readily observed. In the early phases of hypertensive disease, the hypertension is labile, in the later phases it is fixed. In manic-depressive insanity and in paranoia, lability of the symptoms in the early phases is followed by fixation. In Graves' syndrome, when one has the opportunity to note the development of the disease in someone whom he has known well, the same sequence of events is noted. It is apparent that in the hyperkinesis of a psychosomatic disease, there are 5 phases. 1. Constitution. 2. The exaggeration of a normal function. 3. Lability of the exaggerated function. 4. Fixation. 5. Somatic changes. It is in the transition between 4 and 5, that is, the eludication of the mechanisms whereby fixed exaggerated functions results in organic changes, sometimes sufficient even to kill, that one of the main problems in psychosomatic medicine lies.

A much abused expression in the medical writings is the word "unknown" when applied to the causation of the psychosomatic disease. This does not represent modesty on the part of the authors but indicates rather a mechanical turn of mind. For such writers, anything that cannot be tested in a test tube, a blood counting apparatus or an electrocardiogram, does not exist. It is a fact that we

do not know the cause of any disease fully; at most, we are aware of part of the chain of circumstances that bring it about. In psychosomatic diseases we see at least a small part of the chain, but to give a blanket indictment that the cause of a disease is not known because we do not know the entire chain is misleading.

Inasmuch as the human equation always enters into their production, the psychosomatic diseases are essentially diseases of the higher civilizations. Furthermore, evidence is strong that they are increasing, and the prospect is good that they will continue to increase unless social, economic and political insecurity is remedied. Attempt at prophylaxis, I need hardly add, is therefore not encouraging. In the meantime, much can be done by adjustment of the individual with the aid of the many forms of psychotherapy that are available. Unfortunately, psychotherapy has enormous limitations. It is painstaking, time consuming, and expensive, and a large percentage of the afflicted have insufficient culture or intelligence to comprehend it. Above all, psychotherapy is of little avail in the fixed and especially in the somatic phases. In these phases, surgery has done much by methods that reduce the exaggerated function to a lower level. In only one of the psychosomatic diseases can a normal function be completely removed, namely peptic ulcer, and a lasting cure be attained. In the remainder, only a reduction of the exaggerated function to normal levels can be accomplished, a milieu that is still potential for a recurrence. That is why, in psychosomatic disease, management only begins when the operation is finished.

In this sketchy survey I have acted the part both of an attorney for the defense and the prosecutor. It is with some misgivings that I now assume the part of a judge; to give a verdict upon the future of psychosomatic medicine and to suggest a discipline of study whereby it may become a worthy member in the hierarchy of specialties in medicine. Psychosomatic medicine no longer needs an apology; it has long passed that stage. But a discipline is needed so that it will grow strong and lusty and above all that it be protected from its overzealous advocates. I shall therefore make a few suggestions. 1. The greatest need is a wider awareness of the principles and implications of psychosomatic medicine; one does not ask that you believe in it but that you shall be willing to believe. This awareness is essential not so much for the better orientation in a wide variety of diseases that are increasing but rather because it will help create a larger student body than the present handful. Psychosomatic medicine needs internists as well as psychiatrists, and no matter what new blood enters the field that training must be bivalent. When Sydenham was asked by a student to recommend the best book from which to train himself in the practice of medicine, Sydenham replied, "read 'Don Quixote.' " 2. Psychosomatic medicine requires more clinical observation and less dialectic. Repeating words and formulas smacks of Galenical medicine. By observation we do not refer to the mere attainment of a snapshot picture but to a moving picture film of disease; in other words, a biological approach. We would not know that the frog was once a tadpole unless we saw the transformation. 3. The bridging of the transition between the psyche and the soma. This is the most difficult job of all, because the lower animals are not subject to the psychosomatic diseases. Nevertheless, in man, quantitative

methods of measuring different varieties of emotion are possible, and may help in partially bridging the gap. From this point to the initiation of the somatic lesion will require studies on the physiology of the autonomic nervous system by new methods of approach. The discovery of the chemical transmission of nerve impulses, it seems to me, fore-shadows such an event perhaps with a study of the finer shades of cellular pathology. Electroencephalography in the study of emotions is still a compartively untilled field.

I close with the hope that this discourse may help in the promotion of an aspiration that is in the minds of nearly all of us, namely that in hospitals people should be treated and not diseases.

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CHAPTER 22

# UREMIA

The present concept of "uremia" has changed profoundly since its original designation as a symptom complex due to the retention of nonprotein nitrogenous substances in the blood, of which urea is the predominant component. It was soon realized that a large part of the multiple clinical manifestations of "uremia" could not be explained on such a hypothesis, and for a while attempts were made to derive a toxic substance from the blood which would simulate such symptoms experimentally. Needless to say, the results of these attempts have proven elusive and probably will remain so, for the obvious reason that uremia represents a congregate of clinical phenomena consequent upon a host of factors of which the increase of nonprotein nitrogenous products in the blood is only a single, and probably a subsidiary one. As a matter of fact, death never comes from uremia, if one defines uremia in the original sense. Death comes from factors of which azotemia is only one of the expressions. A person therefore may be said to die *in* uremia but not *of* uremia. Hewlett (1) and his co-workers swallowed 100 grams of urea in an aqueous solution over a period of four to six hours. They experienced headache, dizziness, apathy, drowsiness and fatigue, most marked when the urea concentration in the blood was at its maximum of 150 to 160 mg. per cent. They had practically no symptoms when the concentration was between 40 and 150 mg. per cent. A urea content equivalent to about 1 per cent of total body weight is required to cause death in an animal (2), which is far from the maximum ever attained clinically. It is a common experience that urea may be given in doses as high as 100 Gm. daily for weeks to patients for diuretic purposes without any harmful effect. Some supposedly uremic symptoms may even arise in conditions in which there is no increase of these nonprotein nitrogenous substances at all. Azotemia and uremia are, therefore, by no means synonymous. Furthermore, the symptoms and signs of "uremia" do not necessarily correspond to a static change in the organism but represent a biologic progression or a summation of a series of altered biochemical and functional organic changes, so that the time element must always be taken into consideration. These altered biochemical and functional organic changes depend largely upon the topography, nature and intensity of the primary disease.

It is fairly well agreed that, aside from protein destruction, an increase in the

nonprotein nitrogenous substances in the blood is due to diminution in renal function, which is not necessarily caused by gross or even microscopic morphologic destruction of the organ. The subsequent natural history of the disturbed renal function depends upon the nature of the primary insult. These may be classified as 1) extrarenal diseases or factors, 2) diseases that affect the vascular supply of the organ, 3) diseases that affect exclusively the excretory channels of the kidney, 4) localized renal disease.

### 1. EXTRARENAL FACTORS OR DISORDERS

The mechanism whereby renal dysfunction is produced has been aptly called by Fishberg (3) "pre-renal deviation" and he lists the following causes.

(a) *Severe and protracted vomiting.* Even in the absence of obstruction of the alimentary tract vomiting may cause an increase in the nonprotein nitrogen in the blood (4). Such an increase is not always associated with alkalosis, since it is occasionally seen in the cyclic vomiting of children which is accompanied by an acidosis. Its immediate cause is dehydration. Azotemia from any other cause, if accompanied by vomiting, becomes aggravated.

(b) *Prolonged diarrhea.* Azotemia rarely occurs in adults unless the diarrhea is consequent to a disease of the kidney or the excretory apparatus, and under such conditions, the azotemia is primarily renal in origin. In children, however, azotemia from an uncomplicated diarrhea of toxic origin is often observed (5). Dehydration, is probably the immediate cause.

(c) *Hepatic disease.* Since the liver synthesizes urea, there is usually a diminution in the nonprotein nitrogen of the blood in most destructive hepatic disorders. Mann and Magath (6) have shown that in complete hepatectomy the blood urea decreases considerably. Occasionally, however, under certain conditions, azotemia develops. Myer and his colleagues (7) in a series of 180 cases of hepatic disease with jaundice found a moderate increase of nonprotein nitrogen in the blood in 39 per cent and a high increase (over 70 mg. per cent) in 10 persons. This was observed in such maladies as hepatitis, cirrhosis, benign obstruction and in malignant diseases. They found that the increase is due to an associated dysfunction of the kidney and not to an increased breakdown of protein. The prognosis paralleled the degree of azotemia. Another form of the "hepatic-renal syndrome" is the so-called "liver death," following operations on the gall bladder, which is accompanied by an azotemia. Keating, Bower and Priestley (8) ascribe certain of these fatalities to a cholorrhea which results in a profound loss of chloride. The cholorrhea usually follows operations for cholelithiasis and is characterized by the passage of large quantities of bile, circulatory collapse, dehydration and a profound hypochloremia. Dramatic recovery follows the infusion of sodium chloride solution.

(d) *Diabetes.* Azotemia may arise in the comatose stage independent of any associated renal lesion. It usually develops in individuals who have had an unusual protracted ketosis and who become oliguric or even anuric. It is associated with marked dehydration and is usually reversible by intravenous saline in glucose solution and insulin.

(e) *Crisis of Addison's disease.* The cause of the azotemia in Addisonian crisis is not entirely clear, but there is evidence that even in the compensated phase of the disease there is some disturbance in renal function. Talbot and his co-workers (9) found, in 10 patients, disturbances of the rate of absorption of glomerular filtrate and tubular reabsorption capacity for glucose. Renal plasma flow and tubular capacity for excreting diodrast were less affected. Administration of desoxycorticosterone acetate partially corrected, but only temporarily, these deficiencies. Inasmuch as no structural changes were found in their fatal cases, they assume that these disturbances were "functional" in nature. They speculate on the cause, but they do not believe that hypotension can explain their findings.

(f) *Traumatic and post operative shock.* In the shock following extensive burns, after coronary thrombosis, and in acute pancreatitis, azotemia may be severe. It usually is associated with marked oliguria or anuria and the specific gravity of the urine is often low (3) showing that the kidney may lose its concentrating ability in the course of but a few days. The immediate cause of the dysfunction is presumably due to diminished renal blood flow (3). In most cases it is responsive to blood transfusion.

(g) *Large hemorrhages into the intestinal tract.* A moderate transitory degree of azotemia has been reported in such cases, even without shock: in these instances, the azotemia has been ascribed to the increased nitrogen intake from the absorbed blood. Johnson (10), in a well conducted study, reports that after a single massive hemorrhage the azotemia may disappear in three days. He found that a marked rise of nonprotein nitrogen and urea in the blood only arises in patients in whom there is a reduction in renal function as determined by the urea clearance and creatinine clearance tests. There was no change in the serum chloride or $CO_2$ combining power. After the administration of 1200 to 1500 cc. of citrated blood he found only transient and slight rises in patients who had normal renal function, but higher and more prolonged rises in those whose urea clearance test was half the normal. This observation may explain the absence of azotemia in certain patients after a severe gastrointestinal hemorrhage. Corcoran and Page (11) found experimentally that bleeding caused a decrease in renal blood flow through the mechanism of hypotension. The glomerular filtration rate is disproportionately decreased. After transfusion this is restored and is accompanied by an increase in the flow of urine. The probability is strong that in some patients a sufficient grade of shock had been present before the patient came to observation to produce a temporary dysfunction of the kidneys. Indeed, Alsted (12) found impaired renal function in his series, but only in those that were accompanied by shock. The azotemia of hemorrhage has no relation to anemia because it disappears even before there is any rise in hemoglobin or red blood cells (4).

(h) *Various acute infections.* Azotemia may attain an appreciable degree in such cases, especially in pneumonia, and the degree is deemed of value in prognosis. When azotemia is present it is usually accompanied by oliguria. Ob-

viously, an azotemia may arise from a complicating nephritis or cardiac failure, but it occurs even without any gross evidence of such complications. In such instances, the azotemia has been ascribed to increased protein destruction. Inasmuch as renal functional tests are usually not feasible in such grave disorders, we do not know whether renal insufficiency is responsible. Obviously, if vomiting intervenes the azotemia is increased.

(i) *Terminal phases of right heart failure.* In rheumatic mitral disease, for example, azotemia of considerable degree, even 100 mg. per cent, may arise. It is always accompanied by a marked oliguria. When azotemia occurs, the previously good concentration of the urine becomes comparatively low in comparison to the volume of urine passed, as Fishberg (3) has pointed out. Indeed, he regards this phenomenon as invariable in all types of prerenal azotemia, and it can be interpreted only as an evidence of renal insufficiency. In the heart failure of hypertensive diseases, the azotemia, when it arises, is exaggerated by anatomical renal damage consequent to vascular disease.

(j) *Pyloric and intestinal obstruction.* A high grade of azotemia is notorious in either pyloric or intestinal obstruction, and the higher the obstruction the greater the azotemia. Furthermore, this occurs even before vomiting sets in and is observable even in obstruction of the cardia when vomiting cannot occur. There are a number of factors that may give rise to the azotemia. Definite evidences of renal insufficiency have been demonstrated in the human being (13) and in experimental obstruction (14). On the other hand Haden and Orr (15) have shown experimentally, by comparing the total nitrogen excretion with the nonprotein nitrogen in the blood, that in upper gastrointestinal tract obstruction there is a marked protein destruction. Whether due to starvation or to a toxic factor they cannot say. The azotemia has been viewed by some as the consequence of chloride loss because it can be mitigated to a certain extent by the intravenous administration of saline. That chloride loss cannot be the entire cause is proven by the fact that some grade of azotemia usually persists. The beneficial effect of the saline is more likely the consequence of its diuretic effect.

(k) *Gout.* Especially during the acute febrile episodes of gout, there may be a moderate azotemia. The azotemia is related to disturbances in renal function, especially in individuals in the senescent years, when hypertension and vascular disturbances are frequently associated.

These azotemias of extrarenal origin are associated with other and sometimes profound chemical and organic functional changes. In most there is lowered chloride content of the blood, and especially of the sodium content, due to loss from one route or another. There is usually a high carbonic dioxide combining power in the blood with resulting alkalosis. The only exceptions to this are in diabetes (due to retained ketone bodies) and in Addisonian crises (due to retained phosphates and sulfates); under such conditions, there is acidosis, which explains the hyperpnoea so often noted in these maladies. In alkalosis, the most prominent symptom is tetany, which is occasionally observed in prerenal azotemia, especially in those states that are accompanied by prolonged vomiting.

Dehydration is common and is evidenced by a loose dry skin, and in extreme cases, as in diabetic coma, by softening of the eye ball. Dehydration is also reflected in a cyanosis, due to hemoconcentration. In conditions associated with shock, the circulating blood volume is decreased, the peripheral vessels are contracted and peripheral circulatory failure results (3). It is not always easy to assign a symptom or sign to this or that chemical or organic functional change. Moreover, there is a strong likelihood that these clinical phenomena are the results of a combination or summation of these changes. The difficulty is further enhanced by the fact that the underlying disease, whether it be due to a toxin or an infection, a mechanical disturbance or a metabolic disorder, brings in its train a host of clinical phenomena which complicate the picture. But even divorcing the latter factors, it is clear that the symptoms and signs of prerenal azotemia vary according to the underlying disease, and that the term "uremia" must be applied with much elasticity in order to classify these disorders. If one so desires, one might apply the term asthenic "uremia" (16) to this group. The difference between this type and that accompanying renal disorders will be emphasized in the following sections.

In most of these disorders, as Fishberg (3) emphasizes, hypotension with consequent diminution in renal blood flow is an important mechanism in the production of the azotemia.

### 2. DISEASES THAT AFFECT THE VASCULAR SUPPLY OF THE ORGAN

These diseases differ from the conditions we have previously discussed by the fact that the clinical expression is modified profoundly by the associated hypertension. In acute glomerulonephritis, which is commonly viewed as the localized expression of a generalized capillary disease, azotemia may arise, especially if there is oliguria and particularly if there is anuria. The azotemia may attain considerable heights. Nevertheless death from "uremia" is rare. In practically all reports, the diagnosis of "uremia" is based on clear evidences of either hypertensive encephelopathy, retinitis or left ventricular failure, conditions entirely dependent upon the associated persistent hypertension. Such evidences of "uremia" may even subside spontaneously or by appropriate treatment. In the so-called "malignant phases" of glomerulonephritis, the same conditions hold, except that the "uremic" manifestations are usually terminal.

In exceptional instances a chronic glomerular nephritis runs its course without the usual hypertension. In such cases, anuria or a profound oliguria may be terminal and death with profound azotemia ensues, but without evidences of hypertensive encephelopathy, retinitis or left ventricular failure. The manner of death is similar to that which, as we shall describe subsequently, follows bilateral obstruction of the ureters.

In renal disease following long continued essential hypertension, and in which the dysfunction is largely conditioned by vascular disease, the so-called clinical manifestations of "uremia" differ sharply from the azotemia that have been previously described. This is particularly evident in "malignant nephrosclerosis." Most individuals with essential hypertension do not reach this stage,

because they usually die before this event either of cardiac failure or a vascular accident. In "malignant nephrosclerosis," azotemia is usually a terminal event and with few exceptions, is irreversible. But some of the supposed "uremic" manifestations, for instance the retinitis, hypertensive encephelopathy and left ventricular failure, bear no relation whatever to the degree of azotemia. These signs are entirely sequential to the concomitant hypertension, the proof being that they arise only in hypertensive states with or without azotemia. A renal malady unaccompanied by hypertension, no matter how aggravated the evidences of renal dysfunction may be, never develops hypertensive encephelopathy. We have tried to show (17) that hypertensive encephelopathy is associated not only with a high diastolic pressure, but with one that has been persistent for a protracted period. It is always associated with a high pressure in the cerebrospinal fluid, which is consequent to two factors: 1) an increased permeability of the hematoencephalic barrier, and 2) a persistent high venous pressure. The papilledema, which is viewed by some as peculiar to "uremia," is a late result of these two factors. The only sign in "malignant nephrosclerosis" that is directly dependent on azotemia and to no other factor is the so-called "uremic frost." It is unlikely that azotemia alone is responsible for the pericarditis of "uremia," because in experimental animals in whom enormous nonprotein nitrogen figures in the blood can be attained by various methods a pericarditis is never seen. As far as my experience goes, this type of pericarditis is seen only in azotemia consequent to vascular renal lesions. Its pathogenesis is unknown. The "uremic" enteritis also bears no relation to the degree of azotemia. Jaffe and Loring (18) submit strong morphologic evidence that localized mucosal hemorrhages and vascular lesions are primarily responsible. Hemorrhagic lesions of the mucosa of the intestine can be produced experimentally by bilateral nephrectomy or bilateral ureteral ligation (19).

### 3. OBSTRUCTION OF THE RENAL EXCRETORY APPARATUS

Clinically, this follows bilateral ureteral obstruction or narrowing by destructive lesions of the renal pelvis in prostatism, in sulfanilimide poisoning and in post-transfusion reactions. Anuria arising from bilateral ureteral obstruction, either by calculi or by neoplastic invasion, causes a rapid and progressive azotemia, especially of the urea component. The plasma chloride at first mounts rapidly, but later sinks, even to below normal, due to salt deprivation and especially to vomiting, which usually sets in early. The blood pressure remains normal but after some days rises but only to moderate heights. Moderate hypertension also follows experimentally after bilateral ureteral ligation (19, 20) probably by the mechanism of ischemia. On the other hand, after bilateral nephrectomy no elevation of blood pressure occurs. The azotemia is accompanied by marked rises in blood phosphates and sulfates, causing an acidosis which, however, is soon neutralized by loss of salt. Especially interesting and noteworthy is a pronounced rise in potassium (21–24) in animals in whom bilateral ureteral ligation or bilateral nephrectomy has been performed. Hoff, Smith and Mukler (21) noted electrocardiographic findings characterized by an

absence of P waves (which was not due to auricular fibrillation), changes in the T waves and widening of the Q R S complex. These changes were noted only when a certain potassium blood elevation was attained, and corresponded to those obtained by injecting large doses of potassium intravenously. The animals died with cardiac arrest, respiration continuing for a short while after the heart ceased to beat. At autopsy the heart was found in diastole. Since then, the identical chemical and electrocardiographic changes have been observed by Bywaters (25) in crush muscle injuries following blitz bombing and by Fitch and Marchand (26) in two cases of nephritis. Under ordinary clinical circumstances, blood potassium levels never attain the heights necessary to produce these electrocardiographic changes, because potassium is easily excreted. At all events, death in the experimental animals was correlated with a certain increase in the blood potassium level rather than to the degree of azotemia (21).

The clinical expression following bilateral ureteral closure differs profoundly from that observed in vascular disease. It is best observed in cases of closure of the ureters by neoplasm or in sulfanilimide poisoning, whether the latter is due to crystallization in the urinary passages or, as in sulfathiozole poisoning, when no crystallization is found. For some days, the patient feels remarkably well. Later there is drowsiness and headache. Only terminally do vomiting, muscular twitchings, occasionally diarrhea and a moderate elevation of blood pressure develop. Death comes after a short period of coma. Sometimes it occurs suddenly, as in experimental animals and in the cases reported by Bywaters (25) and Fitch and Marchand (26), presumably from potassium intoxication. I have observed a patient with complete anuria for a period of eighteen days consequent to neoplasm, who aside from headache felt well up to within twenty-four hours of death, when coma set in. Myers (27) observed a patient under similar circumstances who lived thirty days. These patients never suffer from hyperpnoea because the primary acidosis is neutralized by loss of base. Because the hypertension is only a terminal phenomenon and never exaggerated, hypertensive encephalopathy, retinitis and left cardiac failure never arise. Similar clinical phenomena occur in post-transfusion reactions (28).

The clinical picture following partial occlusion of both ureters cannot be portrayed because published reports are few in number and not sufficiently well studied. One would surmise that it would depend largly upon the degree and duration of occlusion. Experimentally, Winternitz and his co-workers (19), by compression with Goldblatt clamps of both ureters in dogs, found that there was an irregular rise in nonprotein nitrogen and an inconsistent rise in blood pressure sometimes attaining 80 mm. Hg above the normal. The animals survived between seven and thirty-five days after the procedure. Winternitz and his co-workers were interested in the anatomic changes and further data are not available.

The commonest cause of renal dysfunction due to obstruction of the renal excretory apparatus is prostatism. This is observed only in neglected cases, when the bladder remains distended and back pressure has caused hydronephrosis. An azotemia, sometimes of considerable degree, may arise; this is usually

accompanied by a rise of blood pressure. Both the azotemia and the hypertension drop sharply after adequate drainage of the bladder is instituted. As a consequence, death from "uremia" as the result of prostatic obstruction is much less frequent today than formerly.

### 4. UREMIA IN LOCALIZED RENAL DISEASE

Most of these disorders belong to the group of "surgical kidneys" and include hydronephrosis, chronic pyonephrosis or pyelonephritis, renal tuberculosis and neoplasms. To these we may add multiple cystic disease of the kidney and bichloride poisoning. Inasmuch as the compensatory capacity of the kidneys is great, considerable destruction over a prolonged period must occur before azotemia arises. Unilateral nephrectomy as a rule does not give rise to an azotemia, except perhaps a transient postoperative one, so that a consistent rise in nonprotein nitrogen in the blood after unilateral nephrectomy is strong presumptive evidence that the remaining kidney is affected. Nearly three quarters of the total bilateral renal content may be removed with survival of the animal (29, 30). Under such circumstances there is a temporary rise of nonprotein nitrogen which soon recedes to normal, probably due to compensatory hypertrophy, and it remains so if the animal is kept on a diet not too rich in protein.

Although the above mentioned disorders imply a greater or lesser destruction of the renal parenchyma, the degree of kidney dysfunction that may be associated is not necessarily proportionate to the degree of destruction, because of compensatory adjustments. Furthermore, it depends upon whether the vascular supply of the organ has been diminished by either compression or destruction and whether one or both ureters have been occluded. When, therefore, in the course of these maladies, azotemia develops, the clinical expression of the resulting "uremia" will be modified by whether one or the other of these two factors or both are associated.

(a) *Hydronephrosis.* A unilateral hydronephrosis with the remaining kidney intact, rarely, if ever, leads to an azotemia. If however, the hydronephrosis is of long standing, fibrosis and contraction may occur with resulting hypertension, which in turn may in time give rise to an azotemia. Individuals with bilateral hydronephrosis are specially subject to hypertension, sometimes to an extraordinary degree (31). Under such circumstances, an azotemia may be accompanied by hypertensive encephelopathy, retinitis and left ventricular failure.

(b) *Chronic pyelonephrosis* or *pyelonephritis.* These two lesions are grouped together because morphologically they are nearly always associated. They are especially common in females and arise from either a pyelitis from pregnancy or in childhood. Aside from a persistent pyuria and a progressive lowering in renal concentration, the early course is usually silent. Eventually an azotemia supervenes which is symptomless for many years. Longcope (32) observed one patient who had a persistent azotemia of 70 mg. per cent over a period of four years. In the terminal phases hypertension develops with its consequences. In

a fair proportion, hypertension never develops. The latter succumb as do individuals with bilateral ureteral obstruction. As in hydronephrosis, the intensity of the process depends upon whether the disease is unilateral or bilateral. There have been a number of reports of cure by nephrectomy of hypertension due to unilateral pyelonephritis (33).

(c) *Tuberculosis.* We do not refer to the albuminuria that occasionally arises in the course of pulmonary tuberculosis. This is not associated with much renal dysfunction. The degree of azotemia caused by tuberculosis of the kidney proper depends on whether the process is bilateral or whether it is associated with a hydronephrosis from ureteral involvement, or whether amyloidosis with contraction has occurred. Contraction of the organ with fibrosis, even without the intermediacy of amyloid changes, may occur (31). Rarely, a glomerulonephritis may be a complication. With contraction hypertension may arise, but it rarely attains considerable levels, because of the attendant weight loss and general weakness. Death occurs only exceptionally in uremia. Usually the cause of death is either pulmonary or miliary tuberculosis, cachexia or amyloidosis.

(d) *Cystic disease of the kidney.* Polycystic kidneys are congenital and nearly always bilateral. They vary in the degree of the destructive process so that they may be symptomless and are often discovered only in routine examinations or at postmortem. Clinical manifestations usually arise in the later years. Statistics on the incidence of azotemia or hypertension are necessarily only approximate because the time factor is not taken into consideration. Thus, Oppenheimer (34) who studied a large series found that hypertension occurs in 57 per cent, a urea blood nitrogen of 50 mg. per cent or more in 75 per cent, and a blood urea of 100 mg. per cent or more in about a third of the total. The probability is very strong that more prolonged observation would disclose a raised incidence. The high incidence of hypertension in polycystic kidney is no doubt due to ischemia from destruction or obstruction of the blood supply (31, 35). The blood pressure may terminally attain heights comparable to those observed in malignant nephrosclerosis. In the intermediary phases of the disease, the patients feel comparatively well. I have on a number of occasions over a period of years, witnessed individuals who showed 60 mg. per cent blood urea and over, and who were ambulatory and in fair health. The manner of death depends on the degree and duration of the hypertension. If the hypertension is high and of long standing, retinitis, encephelopathy and left ventricular failure may complicate the terminal picture of "uremia." If hypertension is absent or moderate, the patients die as if they had bilateral ureteral obstruction.

(e) *Neoplasms of the kidney.* Nonmalignant neoplasms rarely cause any serious renal dysfunction. The occurrence of azotemia in malignant neoplasms of the kidney depends not only on the degree of the destructive process but also upon whether a hydronephrosis has been engendered. This occurs in about 20 per cent, according to Kududschanow (36). It also depends upon whether degenerative and fibrotic changes within the parenchyma arise, due to pressure by the neoplasm. The age of the individual undoubtedly contributes because

of the common vascular disease and hypertension incident to senescence. At all events, an azotemia of any degree is exceptional, because the ravages of the disease cause death before any significant azotemia develops.

(f) *Acute mercury poisoning.* The dominant action of mercury is on the tubules, causing destruction and necrosis. The glomeruli show congestion, with occasional exudation into the glomerular capsule (37). Depending on the size of the dose, oliguria followed by anuria occurs somewhere between the fourth and tenth day (38). This is followed by an intense azotemia, a marked lowering of the blood chloride, and a lowering of the alkali reserve with a resulting acidosis, the cause of which is not clear. Howard (38) believes it is dependent on a disturbance of the ketone metabolism (K poisoning?). He has even noted dyspnoea in the terminal phases. The patients die like those with bilateral ureteral obstruction. Indeed, Hayman and Priestley (39) remark on the close resemblance of the blood changes to those observed in experimental bilateral ureteral ligation.

It may be of interest in relation to the subject of azotemia in pure renal involvement that Winternitz and his co-workers found (40) that animals after bilateral nephrectomy live nearly twice as long as those after bilateral ureteral ligation. The reason for this is not clear, but it certainly is not due to the azotemia, since it bore no relation to the degree of the nonprotein nitrogen levels n the blood.

## SUMMARY

It is apparent therefore that of the wide variety of symptoms and signs that have been ascribed to "uremia" in the past, azotemia itself contributes very little to the sum total. The only symptoms that may be ascribed to the azotemia are headache, somnolence, the gastrointestinal symptoms and the uremic frost on the skin. The remainder are in part the consequence of factors independent of the azotemia, notably the hypertension, the elecrolytic disturbances of sometimes totally different patterns, the acidosis or alkalosis, the dehydration, the phenol and potassium intoxications and the diverse dysfunction of one or other parenchymatous and endocrine organs. Such tests as the xantho-protein test, supposedly for phenols, which Belcher devised to distinguish the asthenic form the hypersthenic type of uremia, loses, therefore, much of its significance.

Uremia is compounded of a host of different and often opposing factors, and any attempt at a unifying concept is doomed to failure. For future study on "uremia" it would serve a more useful purpose to try to correlate clinical phenomena in terms of changes in the organism to a particular disease and not to such an abstract concept as "uremia." As a symptom complex, the term "uremia" is as obsolete as the terms "fever" and "headache."

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CHAPTER 23

# NEPHROSIS

Since the introduction of this term into medical nomenclature by Friedrich Müller in 1905 (1), the concept of "nephrosis" has been subjected to so many vicissitudes that today he would not be able to recognize his own offspring. Beginning as an idea, nephrosis has been at various times a unitary pathological lesion, multiple pathological lesions, various clinical syndromes and finally, a single but rare renal lesion with a characteristic clinical expression. No two investigators are agreed as to the strict definition of a nephrosis and the introduction of this term, as with most that have a metaphysical connotation, has created more confusion than otherwise. It is not a disease in the sense that it has a consistent background in pathology. At best, it is a clinical syndrome with multiple morphological backgrounds, not only renal but otherwise. As a consequence of the many adventures that this term has been subject to, one has the right to demand what is meant when this term is employed. Without a definite prefix, "nephrosis" means but very little.

In order to appraise the various evolutions, a brief historical survey is necessary. Müller coined the word "nephrosis" to cover the purely degenerative lesions of the kidney as opposed to the inflammatory. By implication, he referred to the purely parenchymatous or tubular lesions of the kidney, since it was long recognized that these differed clinically from the purely vascular or inflammatory nephritides, edema being the predominant symptom. This attempt at differentiation already involved a number of fallacies. First, because the differentiation was quantitative and not qualitative inasmuch as the inflammatory and vascular nephritides presented tubular changes to a greater or lesser extent and *vice versa*; and second, because to this day the term inflammation has received no precise morphological connotation. "Inflammation" is subject to too many personal interpretations. In fact, Aschoff (2) objected seriously to the term "nephrosis" because to his notion even a degeneration of a cell is an inflammation since it represents a reaction to an injury. In 1913, Munk (3) found in certain patients suffering from what was then diagnosed as "parenchymatous nephritis," with edema as the outstanding symptom, doubly refractile lipoid droplets in the urine and on demonstrating that the tubules of such kidneys contained lipoid material, introduced the designation "lipoid neph-

rosis." He regarded the disease as extrarenal, metabolic in mechanism and ascribed active lues as the main cause. In the meantime, Volhard and Fahr (4) in their classical monograph introduced "nephrosis" as one of the great trinity in their classification of the bilateral hematogenous nephropathies, insuring a foothold for this term that has endured since. Conceiving nephrosis morphologically as any tubular and degenerative lesion of the kidneys, they comprised in their subdivision such diverse lesions as cloudy swelling, fatty and hyaline degeneration, necrosis (mercury poisoning) and amyloid kidney. Since then, other observers have included in their classifications of "nephrosis," the kidney of pregnancy, febrile albuminurias, the kidney in multiple myeloma, the kidney in diabetes and the kidney in jaundice. Volhard and Fahr, however, recognized a clinical entity characterized by tubular degeneration associated with edema and normal renal function which they termed "genuine" or "cryptogenic nephrosis" and which formed an important clinical subgroup. Soon after, came the brilliant investigations of Epstein (5). First, he confirmed the suspicion held by Bright and the actual demonstration by Cstary (6) of a low protein blood content, and of Chauffard and his co-workers (7) who found a high cholesterol blood content in "parenchymatous nephritis" with edema. His outstanding contribution was his application of the neglected law of Starling (8) published in 1896 to the interpretation of the cause of edema. Starling's law is the following: "At any given time there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood in the capillaries for the surrounding fluids. With increased capillary pressure there must be increased transudation—with diminished capillary pressure there will be an osmotic absorption of salt solution from the extravascular fluid." Inasmuch as protein exerts a considerable osmotic pressure, any considerable reduction in the total protein of the blood lowers the osmotic pressure to the point when the hydrostatic pressure, especially in the venous end of the capillaries will become dominant and serum will exude into the tissues. The application of this law into clinical medicine has stimulated extensive and fruitful investigations upon blood proteins both in health and disease. Epstein adopted the term "lipoid nephrosis" as the morphological background of the disease which he had previously designated as a "parenchymatous nephritis," the cardinal clinical features of which were the following: marked albuminuria, hypoproteinemia, hypercholesterinemia, double refracting lipoid droplets in the urine, normal systemic arterial tension, secondary anemia, edema or anasarca with a low protein content of the transudate, normal renal function, a lowered basal metabolism and an exceptional tolerance to thyroid preparations. In numerous publications, Epstein has built up a superstructure of theory and pathogenesis which in many particulars has been confirmed.

The concept of "nephrosis" was a direct challenge to pathologists. It did not take long to discover that clinically and morphologically the results were irreconcilable and that in cases where the clinical mimicry was close, a "lipoid nephrosis" was not always the finding at post-mortem examination but that often a glomerulonephritis, less frequently, an amyloid kidney and rarely, the

sclerotic kidney associated with hypertension were found. For the anatomical diagnosis of these cases, the suffix "nephrotic syndrome" was added to differentiate them from the genuine "lipoid nephrosis." Nevertheless, these kidneys aside from the dominant lesion, revealed the characteristic morphological features of the "genuine nephrosis," namely, lipoid deposition of the tubules and the double refractile bodies both in the urine and in the parenchyma. It was correctly concluded that the lipemia represented the underlying pathogenesis responsible for the lipoid deposition in these diverse morphological backgrounds. In the course of further study, it became apparent that many of the clinical features supposedly characteristic of "lipoid nephrosis" notably, edema, low serum protein, hypercholesterinemia and the low protein content of the transudate, occurred in many disorders in which the kidney was not implicated, notably, in protein starvation (war edema), hepatic cirrhosis with repeated tappings, in prolonged slow bleedings from whatever cause, in pernicious anemia, in prolonged ulcerative lesions of the intestines and in certain cases of sprue or sprue-like conditions. The common denominator in these extrarenal maladies is a hypoproteinemia, the result either of loss, deficient intake, failure of formation and in all probability, deficient absorption of protein. Even in these conditions, the suffix "nephrotic syndrome" is often added to the diagnosis, but etymologically, of course, without the slightest justification.

From this brief historical review, it is apparent that the term "nephrosis" has had various nosological interpretations both clinical and morphological. As a consequence, no two current classifications of "nephrosis" agree. We have already quoted Volhard and Fahr's classification. Munk (9) classifies the nephroses thus: 1) albuminous degeneration; 2) fatty degeneration; 3) lipoid degeneration; 4) necrosis; 5) hyaline degeneration; 6) amyloid degeneration; and 7) glycogenic degeneration. Bell (10) classifies the nephroses into two broad groups: (a) the simple nephroses and (b) the special nephroses. Among the simple nephroses he includes 1) those due to chemical poisons; 2) those due to bacterial poisons; and 3) those due to jaundice. Among the special nephroses, he includes 1) the nephrosis of eclampsia and 2) amyloid kidney. "Lipoid nephrosis" is excluded in this classification because he regards it as a glomerulonephritis. Fishberg's (11) classification is the following: 1) Larval nephrosis, under which he includes febrile albuminuria, diabetic nephrosis, the nephrosis of jaundice, hemoglobinemia, Graves' disease and those due to chemical poisons. 2) The necrotizing nephrosis, notably that due to mercury poisoning. 3) Chronic nephrosis which in Fishberg's interpretation is synonymous with "lipoid nephrosis" and 4) amyloid kidney. Finally, Leiter (12) in an admirable review strictly limits the designation of nephrosis to that conventionally regarded as "lipoid nephrosis" which he regards as suggestive of a primary renal origin. This is a far cry from the original and even transitional designations of this term. Indeed, many clinicians confronted with the maze of conflicting concepts are veering towards Leiter's point of view. The problem narrows down to this. Is "lipoid nephrosis" a biologically pure disease with a consistent etiology, pathology, pathogenesis and clinical expression and course? In order to answer

this question a review of some aspects of the current knowledge concerning "lipoid nephrosis" is necessary.

In the first place, the disease known as "lipoid nephrosis" is rare. In The Mount Sinai Hospital, where there has perhaps been more abundant opportunity to observe "lipoid nephrosis" than elsewhere because of Dr. Epstein's association, only one or two cases that meet the strictest criteria may be seen in the course of a year, mostly on the children's service.

*Etiology.* Since Dieulefoy (13) who in 1899 reported 17 cases of tubular degeneration of the kidney with albuminuria and edema in 17 luetics, mostly in the secondary stage, lues has been a tradition as a cause of "lipoid nephrosis." This tradition received considerable fixation from Munk (9) who in his earliest publication reported the enormous number of 14 cases of "lipoid nephrosis" due to lues. In a more recent edition of his text book (1918, Munk (9) has become somewhat lukewarm in respect to the etiological reaction of lues to "lipoid nephrosis." Reports of most observers give lues a very minor rôle. It seems to me that this tradition has been founded without sufficient critique. In the first place, a history of lues or a positive serological test in a patient with "lipoid nephrosis" does not necessarily imply cause and effect. Experience is replete with such errors in other branches of medicine and mere associations are not taken into consideration. Second, in many of the reports an albuminuria is the only distinguishing mark of the "nephrosis," diagnosticating by inference nothing more than a tubular degeneration. Furthermore, such cases have been reported after the patient has had treatment for his lues, so that it is impossible to assert whether the albuminuria is the result of lues or of treatment. It is true, as Fishberg (11) insists, that neither mercury nor the arsenicals cause sufficient albuminuria to cause edema and that a "lipoid nephrosis" cannot result from treatment alone under any circumstances. The report of a luetic "nephrosis" after treatment has begun is, therefore, manifestly invalid if mere albuminuria is the criterion. In order to ascribe a luetic origin to "lipoid nephrosis" two criteria, it seems to me, are essential. First, that the kidneys at post-mortem examination in syphilitic lipoid nephrosis show either unmistakable lesions of lues or the presence of the spirochete. I have found no instance in which these evidences have been indubitably proven. In fact, in the rare instances of proven luetic involvement of the kidney, a "nephrosis" has not been part or parcel of the clinical picture. The sponsors of the luetic origin of "lipoid nephrosis" evade this issue by assuming that it is the toxin and not the spirochete. Curiously, as far as I can perceive, this is the only instance in all medicine in which the virus of lues has been invoked as the cause of a frankly syphilitic disease. In every other instance, one blames the spirochete. Second, if lues is ascribed as the cause of a "lipoid nephrosis" one should reasonably expect a cure of the nephrosis" by appropriate treatment, inasmuch as the tubular change is a reversible phenomenon, as evidenced by its occasional curability. I have not been able to find one unmistakable proof in any report that this happened. In one case of apparently typical "lipoid nephrosis" associated with a positive Wassermann reaction which I observed many years ago (in passing, it is the only

case in my experience in which lues was suspected), the patient grew steadily worse on antisyphilitic therapy and died of erysipelas following artificial drainage of the leg.

In summary, the causal relation of syphilis to "lipoid nephrosis" must be viewed with much skepticism.

There have been various other causes ascribed to "lipoid nephrosis," notably, infections. I believe the reason for the apparent "cryptogenic" character of "lipoid nephrosis" lies in the fact that "lipoid nephrosis" does not come to observation until long after the initial insult has taken place. "Lipoid nephrosis" like other maladies has a biological course, and the earliest or larval phases we can only surmise, but there is no doubt that a hypoproteinemia, which as we shall see is the dominating agent in the mechanism of "lipoid nephrosis," must persist for a considerable period before the full-fledged picture of "lipoid nephrosis" becomes manifest.

*Pathogenesis of "lipoid nephrosis."* Epstein's application of Starling's law explains most of the clinical phenomena of "lipoid nephrosis." His contention that hypoproteinemia was the basic factor in the production of the edema and anasarca has received full clinical and experimental confirmation (Landis (14), Gorvaerts (15), Leiter (16)). Furthermore, this mechanism has thrown light upon the hitherto unexplained edemas of extrarenal origin. The critical blood protein level at which edema appears hovers around 5 per cent, *other things being equal.* However, it has since been shown that the osmotic equilibrium of the serum depends more upon the albumin fraction than on either the total protein or globulin content, for the reason that the albumin molecule possesses five times the osmotic pressure of the globulin fraction (Loeb (17)). The determination of the albumin fraction is, therefore, of paramount importance. The critical blood level at which edema appears, again other things being equal, is approximately 2.5 to 3 per cent. The inversion of the albumin-globulin ratio which commonly occurs in "lipoid nephrosis" is due to the smaller albumin molecule as compared to the globulin, whereby far greater quantities of the albumin fraction pass into the urine than globulin. For practical purposes this ratio is not important.

There is but little question that the hypoproteinemia of "lipoid nephrosis" is the result of loss of albumin by way of the urine. The loss may be great, even 25 to 30 grams a day. Considering that the total plasma albumin of a man weighing 70 kilos is 140 grams, the drain unless compensated by regeneration is enormous. How much protein may be lost in the urine daily in order to cause hypoproteinemia cannot be answered with any precision because the time factor must be considered. Patients who pass only traces of protein are never in danger of developing hypoproteinemia. To what extent the protein loss occurs by way of the glomeruli or tubules is debatable, and for the interpretation of "lipoid nephritis" a matter of indifference. At one time, Epstein sponsored the theory that "lipoid nephrosis" was primarily the result of biologically altered serum protein but this is hardly tenable in view of the fact that a clinical picture identical with that of "lipoid nephrosis" may be caused by a glomerulonephritis

and other renal lesions in which the assumption of altered serum protein cannot be considered. Furthermore, it renders the not infrequent cure of "lipoid nephrosis," by diet and thyroid and even spontaneously, difficult to understand. Indeed, most observers have found the serum and urinary proteins to be identical. On the other hand, Goettsch and Lyttle (18) recently have reported abnormal albumins and globulins in the serum of nephrotic patients. If confirmed, it still remains to be shown whether this change is primary or secondary.

Hypoproteinemia is not an exclusive feature of "lipoid nephrosis" but part and parcel of a host of other maladies, renal and otherwise. First, it is found in any renal disorder in which a considerable proteinuria is a feature; in glomerulonephritis very commonly; less frequently in amyloidosis and rarely in nephrosclerosis with hypertension. These observations alone negate a metabolic disorder and substantiate a primary renal origin in "lipoid nephrosis." Second, and perhaps more significant, are the hypoproteinemias of extrarenal origin. Some years ago (19), I summarized these disorders under three headings. 1) Those due to loss of protein. In this group belong the renal diseases just mentioned; anasarca of whatever origin, hepatic or cardiac, in whom repeated tappings are necessary; prolonged and repeated hemorrhages, for instance, from a peptic ulcer; and dysenteries in which much serum and blood are lost in the stools. 2) Deficient intake of protein. This occurs in "war edema" and starvation and is especially common in the tropics as the result of an inadequate protein diet; also in chronic alcoholism and in the protein deficiency of horses. 3) Insufficient formation of protein. This occurs in pernicious anemia; in severe disease of the liver and as a secondary factor in "nephrotic states." To this classification I would now add 4) failure of protein absorption. This accounts for the hypoproteinemia occasionally seen in sprue. The final proof of the sequential relation between hypoproteinemia and edema was demonstrated by Leiter (16) by plasmaphoresis. It must be remembered that while hypoproteinemia is the main conditioning factor in producing the edema of "lipoid nephrosis," the edema is to a certain extent modified and controllable by electrolytes, especially the sodium ion. Furthermore, all hypoproteinemias of whatever origin, clinical and experimental, have another attribute in common with "lipoid nephrosis," namely, the low protein content of the edematous transudate, quantitatively proportionate to that found by Epstein in edema of "lipoid nephrosis." This observation incidentally renders highly improbable a mechanism once seriously held, that increased permeability or damage of the capillaries was the cause of the edema in "lipoid nephrosis."

Hypoproteinemia does not limit its sphere of influence in merely creating edema. There is hardly any question but that it bears some relation to the development of the lipemia that is so consistently present in "lipoid nephrosis." The relation is probably an indirect one and as yet, not clearly understood.

In many of the earliest investigations, the lipemia was viewed as secondary to the primary deposit of lipoid in the kidney, thus again suggesting that "lipoid nephrosis" is a metabolic disease, but this view is no longer tenable in view of the fact that a lipemia is just as consistently present in hypoproteinemias of

extrarenal origin. Although there is no direct quantitative relation, a lipemia occurs in practically every disease associated with a hypoproteinemia and even experimentally by bleeding (Fishberg and Fishberg (20)), by plasmaphoresis (Leiter (16), Barker and Kirk (21), and by experimental protein inanition (Weech and Ling (22)). Certain explanations have been proposed for this remarkable correlation; that the lipemia helps to neutralize the lowered osmotic tension (20); that as the result of the protein depletion there is a mobilization of fat from other depots (23) similar to that found in certain cachectic states; that it is the result of the associated anemia. That lipemia does not represent a primary disturbance in metabolism is proven by the observations, first, that it follows and does not precede a hypoproteinemia and second, that in other states associated with lipemia, for instance, xanthomatosis, a lesion even remotely resembling "lipoid nephrosis" is never produced.

It seems to me that the best explanation of the lipemia in "lipoid nephrosis" lies in its relation to the lowered basal metabolism so uniformly found in hypoproteinemic states. The lowered basal metabolism in "lipoid nephrosis" was viewed by Epstein as supporting his conception that it is a metabolic disease and the familiar tolerance such patients possess for thyroid medication seemed to support his contention. He admitted that the differentiation between "lipoid nephrosis" and myxedema was sometimes difficult; indeed, the association of the two has been reported.

In a recent paper (24), I submitted abundant evidence that the lowered basal metabolism in "nephrotic states" could only be explained by the edema which acting as a suit of clothes, prevented the dissipation of heat from the body. Indeed, I showed that any malady associated with integumentary thickening was often accompanied by a lowered basal metabolism, for instance, ichthyosis, the edematous stage of scleroderma, certain cases of congestive failure without active dyspnea or tachycardia and true myxedema. It is a remarkable fact that in all the above mentioned conditions a lipemia as represented by a hypercholestrinemia was invariably present. These observations afford additional evidence that the lipemia in "lipoid nephrosis" is not a primary disturbance in metabolism. The genesis of lipemia in "lipoid nephrosis" may be represented in the following mechanism: hypoproteinemia → edema → lowered basal metabolism → lipemia (hypercholestrinemia). At the same time, these evidences disprove the one time assumption that the lowered basal metabolism in "lipoid nephrosis" is entirely the result of an associated primary hypothyroidism. More likely, the lowered metabolic rate in edematous conditions is at the expense of the extrathyroid moiety of the total metabolism; and whatever effect the administration of thyroid preparations in "lipoid nephrosis" may possess, the result is symptomatic and not specific. The lipemia accompanying lowered metabolic states has all the earmarks of a compensatory phenomenon but the precise teleology is entirely unknown, and will remain so until the function of the stereos in body economy is better understood.

In this rather cursory summary, we have seen that most of the cardinal clinical evidences, namely, hypoproteinemia, edema, low protein content of the trans-

udate, lipemia, lowered basal metabolism and the low osmotic pressure of the blood are by no means the exclusive property of "lipoid nephrosis" but occur in manifold maladies, renal and otherwise, the essential linkage being a hypoproteinemia. The issue that now confronts us is what additional property or properties does "lipoid nephrosis" possess that confers upon it the dignity of a nosological entity? We may exclude the extrarenal disorders at once because they do not enter into the differential conflict and shall limit ourselves to the renal disorders that simulate "lipoid nephrosis."

First, the differentiation is based on clinical grounds. The differentiation of "lipoid nephrosis" from amyloid disease and nephrosclerosis with hypertension affords little or no difficulty. The malady from which "lipoid nephrosis" more often meets difficulty in differentiation is glomerulonephritis. Those who uphold "lipoid nephrosis" as a disease entity contend that glomerulonephritis differs from "lipoid nephrosis" in three essentials; first, the cause of "lipoid nephrosis" is unknown; second, "lipoid nephrosis" is not associated with hypertension and third, renal function is not impaired in "lipoid nephrosis." Let us view these differentials closely.

The factor as to whether the cause of a disease is known or unknown cannot be reasonably employed as a measure of differentiation. We have already discussed one of the reasons why the cause of "lipoid nephrosis" is unknown, namely, that the patient only comes to observation long after the initial insult. The opportunity to observe the biology of the disease from its very inception is most desirable. Furthermore, although the probability is strong that an infection, usually the streptococcus, initiates a glomerulonephritis (the mechanism is still not clear), in the vast majority of instances especially of the chronic type, the cause is not obtainable, at least in our experience. However, this is no bar to the diagnosis. The question of elevation of blood pressure is important for the differentiation between "lipoid nephrosis" and glomerulonephritis, *provided it is present.* Whether hypertension may be absent throughout the *entire* course of a proven glomerulonephritis is questionable but that it is absent at some particular cross section of the life cycle is a familiar observation. I have repeatedly witnessed the disappearance of hypertension in the subacute or chronic stage of a glomerulonephritis. Had the presence of hypertension escaped us, the diagnosis of "lipoid nephrosis" in those who presented a "nephrotic syndrome" would have been perfectly justified. The absence of renal insufficiency in "lipoid nephrosis" would also be a justifiable differentiation from glomerulonephritis provided that renal insufficiency is an invariable accompaniment of glomerulonephritis, but it is well known that the milder types of chronic glomerulonephritis may persist for many years without any evidence of impairment of renal function.

In the last analysis, therefore, these clinical differentials are entirely arbitrary, and do not take into consideration the possible biology of the disease.

*Pathology.* Finally, the standing of "lipoid nephrosis" as a disease has been based on a distinctive morphology. It is admitted that the deposition of lipoid, mostly doubly refractile, in the epithelial cells of the tubules and to a certain

extent in the glomeruli and interstitium, is not the specific lesion of lipoid nephrosis inasmuch as this deposition is also found in glomerulonephritis and amyloid kidney with a "nephrotic" tendency. The specificity of the lesion of "lipoid nephrosis" is supposed to depend not only upon the comparative integrity of the glomeruli but also *upon the absence of morphological changes conventionally recognized as those of a glomerulonephritis.* In view of the striking clinical mimicry between the two diseases, many distinguished pathologists have suspected that "lipoid nephrosis" is the result of a glomerulonephritis and much controversy has raged upon the interpretation of glomerular changes that have been observed in "lipoid nephrosis." There is no need to review the pros and cons of these debates; the conclusion is invariably reached that the minimal glomerular lesions in "lipoid nephrosis" are not comparable to those found in the ordinary types of glomerulonephritis. The matter remained dormant until recently when Bell (25) revived the controversy. Employing a histological technique of MacGregor, Bell described in four cases of what he believed to be "lipoid nephrosis" a thickening of the basement capillary membrane and a varying increase in the number and size of the glomerular endothelium lesions which he interpreted as a glomerulonephritis. Bell's conclusions have been criticized, for instance, by Leiter (16) on the ground that none of his four cases appeared to be unalloyed instances of pure "lipoid nephrosis" clinically. In all probability they were cases of glomerulonephritis with a "nephrotic component." Kantrowitz and Klemperer (26) with the same technique found no semblance of a glomerulonephritis in undoubted "lipoid nephrosis."

The matter does not rest here. Because the kidneys do not show the conventional histological lesions of glomerulonephritis does not necessarily imply that *such lesions may not previously have existed.* The entire problem hangs upon whether our knowledge of the morphological evolution of the lesions of acute glomerulonephritis is complete. This is far from being the case. 1) We are well informed of this evolution in clinically progressive chronic glomerulonephritis whether associated with a nephrotic component or otherwise, but we are still entirely unacquainted with the morphological appearance of the glomeruli in clinically healed cases. Being largely a productive inflammation with proliferation of the intra- and extra-capillary endothelium of the glomeruli as the predominant lesion, some have presumed that complete restoration to the normal is never completely attained. This question still awaits solution. After a diligent quest extending over many years, I have not been able to find such a kidney. 2) We now come to the crux of the problem. For years, clinicians have observed that occasionally clinically established cases of acute glomerulonephritis lose their hypertension, renal insufficiency, etc., and eventually develop the typical clinical picture and course of "lipoid nephrosis." At times, even complete recovery ensues. While such observations are not common I have observed perhaps half a dozen in the course of the past twenty-five years. What glomerular lesions may we expect to find in such an instance? The only case that satisfies the above mentioned clinical requirements and that has come to postmortem examination at The Mount Sinai Hospital is the following. Further-

more, this case presented the first opportunity to study the development of a "lipoid nephrosis" from its very inception to its terminal phase.

## CASE REPORT

*History* (Adm. 461645). R. H., age 3 years, was first admitted December 3, 1939. The child had been sick with fever and sore throat for a week, swelling of face and abdomen for two days, and red urine for one day. There was moderate swelling of face and legs. The temperature was 103°F., but returned to normal the next day. There was evidence of receding tonsillitis. The blood pressure was 140 systolic and 100 diastolic; the blood urea nitrogen was 8 mg. per 100 cc.; the serum protein was 5.1 per cent of which the albumin fraction was 3.8 per cent. The urine contained albumin 2 plus, red blood cells and a few casts. On December 5, it was noted there was no gross blood in the urine. On discharge, December 19, 1939, albumin had disappeared from the urine. On February 1, 1940, in the follow-up clinic, the patient gave a history of having had "grippe" two weeks before. Moderate edema was noted over the tibia, the urine contained albumin 2 plus, the blood pressure was 120 systolic and 80 diastolic.

*Second admission* (March 12, 1940). Three weeks before admission generalized edema was noted. The blood pressure was 124 systolic and 90 diastolic; the blood urea nitrogen 9 mg. per 100 cc.; the total serum protein 4.5 per cent of which the albumin fraction was 2.5 per cent; and the cholesterol 550 mg. per 100 cc. The child was placed on a high protein diet and given 8 grains of thyroid without effect. During her stay in the hospital the edema persisted, the urinary albumin was 3 plus, the cholesterol was high, on one occasion attaining 1050 mg. per 100 cc. The blood pressure remained about the same. There was one attack of abdominal pain with fever. The patient was discharged August 6, 1940.

*Third admission* (August 25, 1941). No clinical improvement was noted during her home stay. The blood pressure was 110 systolic and 85 diastolic. The serum protein was 3.3 per cent of which the albumin fraction was 1.5 per cent. The blood chemistry was the same as on the last admission. The child had erysipelas twice. The child died of a pneumococcus peritonitis on January 12, 1942. (The urine always contained 4 plus albumin with a few red blood cells and rare casts.) Two weeks before death the blood urea nitrogen was 28 mg. per 100 cc.

*Necropsy findings* (P.M. 11728). The renal architecture of the *kidney* seems not to be profoundly disturbed; however, throughout the cortex one sees small foci of tubular atrophy with increased stroma and frequently one sees the stroma widened with infiltration by lymphocytes with occasional polymorphonuclear leucocytes. The first convoluted tubules are quite distended and contain a considerable amount of albumin. The epithelial cells generally show a good brush border and the cytoplasm is finely granular. The terminal portion of the convoluted tubules contains a large amount of pink granular material which is probably albumin. The epithelium in such portions shows vacuolization. *Glomeruli:* A superficial examination of the glomeruli seem to indicate that they are not materially altered. However, if one examines more carefully, one finds certain changes affecting the majority of the glomeruli. The lobulation of the tuft is exaggerated and the lobules appear rather plump. The basement membrane of the capillary loops are quite thick and there is fusion of such loops with each other and with the capsule. Some glomeruli show multiplication of the capsule epithelium. The Bowman's space contains only a small amount of albumin.

The two kidneys together weighed 240 grams. They were enlarged, white-yellow and soft. The capsule stripped with ease. There is no scarring, hemorrhages or granularity of the surface. On section, the cortex and medulla are sharply demarcated. The glomeruli are visualized as pin-point red dots.

## COMMENT

It is apparent that the changes in the glomeruli that are not completely intact correspond closely to those described by Fahr (27), Munk (9) and others in "lipoid nephrosis," even in regard to their focal distribution. In addition, there was thickening of the basement membrane as described by Bell (26). The histological changes of the previous glomerulonephritis have almost completely resolved except for a minimal proliferation of the capillary endothelium, thickening of the basement membrane and occasional fusion of the glomerular loops. In other words, this kidney might be regarded morphologically as characteristic of "lipoid nephrosis" *provided we were not aware that the patient had previously passed through a well established acute glomerulonephritis.* In other words, we have witnessed in this case the evolution, both clinical and morphological, of acute glomerulonephritis to "lipoid nephrosis." Had this patient been seen for the first time during the third admission, the diagnosis of "lipoid nephrosis" would have been, according to present criteria, perfectly correct which again substantiates our conclusion that the majority of patients with clinical "lipoid nephrosis" come to observation only after the initial phases have passed. In short, a correct interpretation of "lipoid nephrosis" requires a complete survey of the biology of the disease, both clinical and anatomical.

Obviously, we are in no position to assume that a glomerulonephritis is always the basic pathology of clinical "lipoid nephrosis" but the possibility is strong that this sequence is exceedingly common. This would account in a measure at least, for the rarely reported instances of "nephrotic contracted kidney." That glomerulonephritis cannot account for all the cases of "lipoid nephrosis" is instanced by a case of bilateral thrombosis of the renal veins with a complete clinical picture of "lipoid nephrosis" that was observed at The Mount Sinai Hospital a few years ago.

On all *a priori* grounds, as we have tried to convey in our discussion of the pathogenesis, a primary renal origin of "lipoid nephrosis" is almost an inevitable conclusion. Nevertheless, clinical "lipoid nephrosis" is by no means synonymous with anatomical "lipoid nephrosis."

## SUMMARY

Historically, the term "nephrosis" has meant many things; a non-inflammatory and degenerative renal lesion, an arbitrarily defined clinical concept, a syndrome associated with multiple backgrounds in pathology both renal and otherwise and finally, a delimited disease with a single background in pathology designated as "lipoid nephrosis." The fundamental characteristic clinical phenomena of "nephrosis" are reviewed and their pathogenesis outlined. The primary factor is a hypoproteinemia which may be the result of loss, deficient intake, insufficient formation and poor absorption of protein. The hypoproteinemia is responsible for the edema and anasarca and for the low protein content of the exudate. In addition, the hypoproteinemia is indirectly responsible for the low basal metabolism by creating an edema which acts as a suit of clothes

preventing the dissipation of heat. This is in conformity with the observation that all integumentary thickenings are usually accompanied by a low basal metabolism. The lipemia of "nephrosis" represents, in all probability, a compensatory phenomenon for the low metabolism, inasmuch as a lipemia is also the usual accompaniment of many edematous states and of integumentary thickenings The validity of "lipoid nephrosis" as a distinct disease entity depends on whether it possesses a precise background clinically and morphologically. Clinically, "lipoid nephrosis" can be differentiated from conditions that simulate it only by arbitrary criteria. Anatomically, "lipoid nephrosis" has no specific or consistent background. There is evidence that in certain instances the lesion of "lipoid nephrosis" represents a glomerulonephritis in which almost complete resolution has occurred. Clinical and anatomical "lipoid nephroses" are by no means synonymous. In the last analysis, "nephrosis" is not a disease and requires precise definition when the term is employed.

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CHAPTER 24

# THE HYPERKINETIC DISEASES

Nosologically, maladies in which the cause is reasonably clear may be broadly classified into five groups: 1) congenital abnormalities of tissue or of chemical metabolism; 2) diseases of endocrine origin; 3) the deficiency diseases; 4) others resulting from exogenous factors (something foreign, a toxin, a trauma, a bacterium, for instance, has invaded the organism resulting in disordered anatomy and function); 5) the hyperkinetic diseases which are predominantly endogenous in nature. In this group, the maladies arise largely conditioned by psychosomatic factors, the result of the impact of environmental influence upon a constitutional background. In these diseases there is a primary exaggeration of normal functions while marked anatomic changes follow. It has hitherto been difficult to recognize that disordered function may sometimes precede morphologic changes, because of the hitherto domination of the Continental School which taught that morbid anatomy precedes changes in function. The concept of hyperkinesis is important for the interpretation and integration of a group of maladies whose etiology is conventionally regarded as uncertain or unknown. Furthermore, these diseases are increasing rapidly, as hospital morbidity statistics eloquently testify; and, because of their prolonged and recurring nature, contribute in a large measure to the increasing cost of sickness.

In order to elucidate this thesis, we shall consider some of the normal body functions and try to show how their exaggerated trends represent the dominant expression of certain well-recognized diseases and, how, with the initiation of the hyperkinesis, there results an orderly biologic progression of the disease from a larval to the fully fledged type.

1. *Normal Intra-arterial Pressure.* Its exaggerated phase is hypertension of the greater and pulmonary circulations. In this report we shall refer only to hypertension of the greater circulation. In a recent publication (32), I discussed the currently recognized causes. These are arranged in what I regard as the order of frequency: 1) psychologic; 2) persistent Graves' syndrome; 3) renal; 4) adrenal blastomata or paraganglioma; 5) congenital peripheral resistances;[1] 6) increased intracranial pressure; 7) carotid sinus; 8) lead poisoning; 9) Cushing's

[1] The term congenital is used purposely to include the cases of congenital stenosis of the aortic isthmus.

syndrome; 10) obesity. Of these, all but the hypertension arising from the first two factors represent processes in which morbid anatomy precedes the exaggeration of function. In the first two, *i. e.*, hypertension of psychologic origin and that occasionally following persistent Graves' syndrome, the hypertension represents the primary process in the sense that it is the earliest clinical manifestation, so-called "essential" hypertension. Elsewhere (33) I have detailed the factors that condition the initiation. Physically, hypertensive individuals tend to be soft muscled, unathletic in type and bodily movement, pudgy, short-necked, ungraceful and overweight. There is a definite relation between obesity and hypertension (17). Physically, they are the antithesis of the child in mental makeup. They do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation. That heredity is a factor in the production of hypertension has been well attested (40, 51), but in how far the hypertensive constitution is genotypic or phenotypic is still problematical. No one can deny that there has been a definite increase in essential hypertension in recent decades, as the present appalling mortality from the cardiovascular-renal syndrome testifies. I have elsewhere (33) discussed the influences that have brought about this increase. Briefly, I believe they may be explained, at least in part, as a by-product of modern civilization, of the stresses and strains that modern living entails. Testimony for this statement is the striking increase in modern times of hypertensive disease in the northern Negro (25), whereas in his native habitat in the heart of Africa, hypertension is unknown (15). It probably is not diet, because diet, except in so far as it is high caloric, does not induce hypertension. Moreover, the diet of northern Negroes has not changed. It cannot be climate because this has not varied. I suspect that the reason may be industrialization and the competitive forces of modern civilization.

In other words, essential hypertension of the greater circulation, like infection and other disease conditions, is the resultant of a background and an insult. Either factor alone is insufficient.

The ultimate anatomic consequences of essential hypertension of the greater circulation are familiar—arteriosclerosis and eventually the catastrophic evidences of the cardiovascular-renal syndrome. The sequential relation of hypertension to arteriosclerosis and its attendant anatomic phenomena has been questioned, because the decrescent or senile type of arteriosclerosis occurs even without hypertension. These observers forget that hypertension is not an absolute but a relative value and that it is merely an exaggeration of the normal intravascular tension which by itself, given sufficient time, will produce arteriosclerosis. The evidence for this point of view lies, as I have pointed out (34), in the independence in incidence between arteriosclerosis of the greater and lesser circulation. Gross arteriosclerosis of the pulmonary artery occurs almost exclusively in conditions in which a hypertension of the pulmonary circuit can be predicated, such as mitral disease, emphysema, etc. Now inasmuch as the normal pulmonary pressure is only one-sixth that of the aorta, the probability is

very strong that even under extreme conditions, the pressure in the pulmonary circuit never approaches the normal pressure in the systemic circuit. The conclusion is obvious that if pressures less than the normal aortic pressure can produce arteriosclerosis in the pulmonary circulation, the normal systemic pressure, given sufficient time, can produce the decrescent or senile type of arteriosclerosis of the greater circulation. The following equation was therefore suggested to cover some of the factors: arteriosclerosis = intravascular pressure $\times$ time. There are, it is true, secondary conditioning factors involved in the genesis of arteriosclerosis, for instance, the chemical composition of the blood, the vascular supply of the walls of the vessels, intravascular stresses and perivascular resistance (32); but these factors merely modify the lesion and affect its distribution. Apparently, normal intravascular pressure is the only normal function that has been shown to give rise to anatomic and sometimes to actual clinical disease. In this sense, arteriosclerosis (at least anatomic but not necessarily clinical) is the inevitable destiny of all animals who have a vascular system such as our own (Chart 1).

CHART 1

*Possible Anatomic and Clinical Sequences*

| | | |
|---|---|---|
| Normal tension<br>Hypertension | Arteriosclerosis | Brain (cerebral arteriosclerosis; apoplexy).<br>Retina: retinopathy.<br>Heart: coronary disease; arteriosclerotic valvular disease; myocardial insufficiency.<br>Pancreas: capillary fibrosis of islands of Langerhans (diabetes)<br>Splanchnic arteriocapillary fibrosis.<br>Kidney: arteriocapillary fibrosis; nephrosclerosis.<br>Extremities: arteriosclerotic gangrene.<br>General arteriosclerosis; cachexia; atrophy. |

This chart explains why visceral arteriosclerosis even though patchy in its distribution is only exceptionally single in its clinical manifestations.

Inasmuch as the principal process disturbed in Graves' disease is the basal metabolic rate, we shall discuss the syndrome more fully under that functional heading. At this time, we need only point out that hypertension of the greater circulation is one of the possible sequences of uncured or spent Graves' syndrome. In the earliest phases, the systolic pressure is usually elevated with a low diastolic pressure, probably due to the shunt engendered by the enormous increase in vascularity of the thyroid gland (7). If the malady persists, these pressures no longer are labile and become more or less fixed. Eventually, both systolic and diastolic pressures rise and, in the course of many years, the cardiovascular-renal syndrome arises in one or more of its manifestations. It has been my fortune to have observed this sequence of events in a considerable number of instances, especially in older patients afflicted with persistent Graves' disease. Page (41) describes a syndrome, usually occurring in young women with essential hypertension, characterized by a high-strung temperament, tremor, tachycardia, perspiration, slight enlargement of the thyroid gland, sensitivity to cold and a

slightly elevated basal metabolism, which he believes is due to diencephalic stimulation. His description certainly fits that of Graves' syndrome and I suspect that this disease is the cause of their hypertension. Inasmuch as I have tried to show (*v. i.*) that Graves' disease is largely a personality disease, the psychogenic origin of some cases of essential hypertension cannot be ignored. The fact remains that Graves' disease may occasionally be followed by the same clinical sequelæ as those of essential hypertension.

2. *Basal Metabolic Rate.* The disease in which hyperkinesis, *i. e.*, increased basal metabolic rate, is a dominant expression is Graves' disease.

In a previous paper (35) I tried to show that Graves' disease is not a nosologic entity in the sense that it has a consistent background in morbid anatomy and a clear etiology, but rather a series of disorders arranged in a biologic progression that have received different eponyms in the past. The natural history of the disease usually extends over a long period. The earliest phase has been called Basedowid, autonomic imbalance, pre-Basedow, neurocirculatory asthenia,[2] etc. The middle stage has been termed "formes frustes," while the final stage is that conventionally termed "Graves' disease" with the characteristic quadrad of symptoms, *i. e.*, tremor, tachycardia, enlarged thyroid gland and exophthalmos, plus an elevated basal metabolic rate. Between the larval and the final florid form, one finds various combinations of signs and symptoms. For these reasons, the term "Graves' syndrome" is regarded as preferable. The proof of this statement lies in the fact that not only are such forward transitions frequently observed but, more frequently, regressions to the larval phases under the influences of either spontaneous remissions or of treatment.

I believe it is a fallacy to regard hyperthyroidism, as measured by the basal metabolic rate, as synonymous with Graves' syndrome. Graves' syndrome contains many clinical elements that are not explainable by the elevated basal metabolism alone. To regard the measurement of the basal metabolic rate as the sole diagnostic test of Graves' syndrome is arbitrary and not warranted by clinical facts for the following reasons: 1) Patients with so-called "spent" or "burnt out" Graves' syndrome who reveal the typical quadrad of signs may possess a basal metabolic rate within the normal range. 2) After a subtotal thyroidectomy which usually reduces the basal metabolic rate to normal, many of the clinical manifestations may persist for years, even though the patient is economically and perhaps socially restored.[3] 3) During the larval phases the

[2] There has been much debate whether "neurocirculatory asthenia" is the earliest stage of Graves' syndrome. We have records of at least a dozen cases at the Mt. Sinai Hospital where at first admission the diagnosis of neurocirculatory asthenia was made, and at second admission Graves' syndrome, in both instances on conventionally recognized criteria. Furthermore, on regression of the Graves' syndrome, a residuum of signs and symptoms often persists that is indistinguishable from neurocirculatory asthenia. As this exposition proceeds, we shall see the close relation of both to states of fear, whether in war or civil life. In a subsequent communication this topic will be discussed more fully.

[3] It is occasionally an exceedingly difficult problem to estimate what is meant by "cure" in Graves' syndrome. In my experience, it is exceptional to get a complete *restitutio ad integram* in this disease. One or a number of the original quadrad of signs and symptoms usually persist.

basal metabolic rate is usually normal; but when, under the influence of an emotional strain, the disease assumes the florid form with a rise in the basal metabolic rate, are we justified in saying that a different disease has been born? All we may say is that hyperthyroidism has entered the picture. 4) The administration of toxic doses of thyroid gland mimics but by no means completes the clinical picture of Graves' syndrome. There is elevation of the basal metabolic rate, tremor and tachycardia and perhaps loss of weight but no exophthalmos or swelling of the gland. 5) Cases with clinical evidences of Graves' syndrome associated with myxedema occur rarely (30). These mostly represent exhaustion phenomena. Hyperthyroidism as measured by the basal metabolic rate may be regarded as a sign, probably the most important of Graves' syndrome and as a measure of the activity of disease, comparable to fever in infections. When the temperature of a patient with typhoid fever returns to normal, he has not necessarily lost his disease.

The common denominator in these various phases is a characteristic personality. In no disease that I am aware of is the personality so indissolubly bound with the clinical manifestations as in Graves' syndrome.

If the patient has been well observed before the onset of the disease or if his personality is reconstructed afterward, he will be found to conform to a vast race that may be described in general as the sensitive, emotional type; furthermore, this personality persists no matter what treatment is instituted, although clinical evidences of the disease have been eliminated. I regard the personality of the patient with Graves' syndrome as so characteristic that, in doubtful cases, the elucidation of the personality serves as a diagnostic measure. Phlegm and Graves' syndrome are, in my experience, antagonistic. Occasionally, one observes patients who appear to have a phlegmatic temperament but when one digs deeper, one finds that it is only a mask.

There are no anthropologic signs that are characteristic of the disease. However, in the constitutional phase these patients present, as a rule, a number of physical signs which represent the larval phases of the future characteristic quadrad of signs. Their eyes stare and are bright and they show more of the whites, especially in action or under emotional stress. During emotion, also, the pulse rate rises to excessive heights and there is tremor. In women, the neck tends to be fuller than normal and under emotional strain, especially during menstruation, when women are usually more touchy, they confess that their throats are larger. Their basal metabolic rate while within the normal range, usually, in my experience, veers to the plus side. Dermographia is nearly always present. These people are exceedingly touchy and respond to their environment like an Æolian harp. A look or harsh word upsets them easily and often irretrievably. As a consequence, they are usually intolerant. They are shy and introvert and live a life of escape. Their personalities have an unusual manic-depressive trend, sometimes even to the edge of a psychosis. They are quick in their movements and mental process. They are prolific day dreamers and idealism plays a large rôle in their mental life. They show a leaning toward the mystic and reveal the artistic temperament, so that in this group one frequently

finds poets, writers, painters. Charm is a salient characteristic. They are usually bad sleepers. In my experience, they respond badly to thyroid preparations as opposed to those of phlegmatic temperament. They commonly relate that in their childhood a nervous disorder followed a slight emotional upset, such as a recitation or school examination. They tire easily mentally and physically. They are sensualists and live on stimulation, emotional, physical and even chemical. They easily become drunkards or drug addicts; indeed, suicides are by no means uncommon. These patients belong to what Kretschmer calls the "cyclothymic" constitution.

In no disease is a study of the immediate family so illuminating. The same malady afflicts two or more members of the family more than the normal law of averages allows and, what is particularly significant, few of the siblings are adjusted and phlegmatic. Most suffer from various forms of neuroses, and manic-depressive trends are common (6). In how far these tendencies are genotypic or phenotypic, I am not prepared to say but from the study of numerous families, I believe that environmental influences, especially overprotection, play the dominant rôle.

In the majority of instances, the onset of the fully fledged disease is ushered in by a psychic insult for which the patient was more or less unprepared, for instance, a robbery, a fire, the death of a close relative, an unrequited love affair, a terrible confinement, a frightful sexual episode, a sudden economic loss, an unwanted pregnancy, are some of the insults that I recall. There was a sudden crop of cases of Graves' syndrome in Vienna after the theatre fire horror in 1884 and in San Francisco after the earthquake. We were particularly struck in the Mt. Sinai Hospital with the frequency of Graves' syndrome in German refugees, so that the term "Hitler Graves" came into vogue. The essential ingredient in this insult is fear. Less often, the disease arises from slow and reiterated insults and the transition between health and disease is indefinable. At times after a sudden shock, the malady reaches its fruition even within a few days.

If the opportunity arises to observe the development of the malady in a person whom the physician has previously known, he will note that the disease represents an exaggeration and fixation of previous trends. A pulse that was normally fast, especially under an emotional stimulus, beats faster. The wide eyes become exophthalmic; a tremor which was previously noted only under excitement becomes exaggerated and constant and the previous emotionalism and instability of temperament is intensified. The basal metabolic rate is now definitely elevated.

This sensitive, emotional personality accounts for a number of things that have interested students of the disease: 1) The greater preponderance of Graves' syndrome in the female. 2) The rarity of the disease in children, in whom the subtler emotive powers are not fully developed. 3) The rarity of the disease in primitive races or in those of crude fiber. As in hypertensive disease, there has been in our experience at the Mt. Sinai Hospital, a decided increase of the disease in northern Negroes since they became sensitized by contact with the white

race. 4) The rapid increase in Graves' disease in recent decades owing to the increased "strain of living," the resultant of increased protective mechanisms (36).

The psychogenic background of Graves' syndrome also explains the freedom of the lower animals from this disease because civilization has not affected them. Indeed, the complete disease cannot be experimentally reproduced—only individual signs and symptoms. The instances in which it has been reported are of doubtful validity. Graves' syndrome is essentially a human disease and especially one of the higher civilizations.

Some years ago. Lorand and Moschcowitz (28) published a psychoanalytic interpretation of Graves' syndrome. They found that: "already in childhood their adjustment to the members of their family was unsuccessful. On the one side they were too much pampered by the parents, especially by the mother, and on the other side, too great a demand was put upon them in the course of their development to which they could not adjust themselves as a result of their earlier protective environment. The vast majority of such patients may be said to have been sensitized to life. They were so shielded in their childhood that when they reached adult age they could not face the conventional tribulations of every-day life with equanimity. They had difficulty in making decisions upon ordinary matters and were infantile in their reaction to life. There was a continual escape from every-day realities and, in consequence, these people would aver that their life had been an unusually hard one. The relation in childhood to the siblings as illustrated in certain cases is even carried over to adult life; for instance, the older sister replaces the father or mother to the other children. In their adult environment they showed the same type of emotional reactions to the attachments and frustrations as they did in childhood. Sexual difficulties, degrees of maladjustment, frigidity in women, fear of pregnancy and fear of childbirth combined with intense resentment and repressed aggression against men were present in all the patients. The unmarried girls showed a type which we can describe as psychosexual infantilism. Their childish attitude about sex matters, their more or less abnormal reaction and feelings concerning their menses, their attitude concerning marriage and sex in general lack all the judgment of the normal adult.

"Their relation and their reactions to their employers show an exact parallelism to their early reactions to their parents. The traces of their earlier emotional fixation to the parents were so obvious in their adult attitude to society that it could not be overlooked.

"In the male patients, whether married or unmarried, the same situations exist. Degrees of sexual impotentia, or at least difficulties in their sexual adjustment, were always present. The masturbation of puberty was continued by some of them up to marriage, partially on account of fear concerning sexual infection and partially as a result of their difficulties in their adjustment to the other sex. Coitus interruptus in the married patients was practiced for a long period of time to meet the demands of their wives in order to prevent impregnation, and at the same time, this sexual dissatisfaction caused resentment against

the sexual partner. It then resulted in a tendency to stay away from intercourse or a strong drive toward unfaithfulness, with implications of fear and feelings of guilt."

The recognition of the individual and his environment is fundamental in the therapy of the disease. The human equation remains no matter what therapy is undertaken, and the impact of the two constitute a potential for a recurrence of the disease. It is futile to discharge a patient after a subtotal thyroidectomy without taking into consideration the ability of the patient to meet the ordinary stresses of every-day life and the environment to which he returns. Indeed, the lesson taught by these recurrences is that the treatment of the patient begins only when the operation has been finished. Although the constitution and the environment appear essential in the mechanism of production of Graves' syndrome, there must be another factor or at least a compensating mechanism, for the reason that sometimes one observes patients in whom despite the presence of both these factors, a Graves' syndrome did not develop.

When the disease is full blown to the stage of so-called toxic goiter and continues more or less fixed, there may be a number of eventualities. We have

CHART 2

*Clinical Evaluation of Graves' Syndrome*

| | | |
|---|---|---|
| Constitution → formes fruste → Graves' syndrome | Persistent tachycardia<br>Arrhythmia; auricular fibrillation | →Myocardial insufficiency |
| | Hypertension<br>Acute thyrotoxicosis | See Chart 1 |

Synonyms: Basedowid. Autonomic imbalance. Pre-Basedowid.

already referred to the possibility of a progressive hypertension and its potentialities. In addition, the persistent tachycardia or the onset of a cardiac arrhythmia, especially auricular fibrillation, may result in myocardial insufficiency. Finally, of course, the disease may lead to death with the symptoms of acute thyrotoxicosis, namely, tachycardia, vomiting, diarrhea, progressive elevation of bodily temperature, emaciation and acidosis.

3. *Normal Gastric Acid and Secretion.* The exaggerated phase is hypersecretion and hyperchlorhydria. The disease in which hyperchlorhydria is most often associated is peptic ulcer.

The cause or causes of peptic ulcer are obscure, but the view is steadily gaining ground that in the background is a constitution that represents a combination of physical and psychogenic characters. The physical characters have been described by Draper (16). They have the "lean and hungry look" of Cassius, the expression is hard and tense, the eyes deep and sullen, the lines of the face are sharply drawn, the mouth is firm, the jaws sharply angled and the masseter muscles are prominent. These patients are usually cyanotic and show a tendency to erythremia. To what extent these physical characters are phenotypic or genotypic is as yet impossible to estimate.

Psychologically, in my experience, the vast majority of ulcer folk conform to a certain type of personality. They are intolerant, all or nothing, self-absorbed and mentally inelastic folk with strong aggressive, masochistic and sadistic tendencies. They harbor strong grudges and it takes them long to overcome any emotional strain. Even their humor is sadistic. They have a paranoid trend. They are haters and fighters.

As in Graves' syndrome, one finds with remarkable frequency that preceding the onset of the clinical symptoms, the patient passed through a period of emotional conflict; the illness or death of a relative, economic distress, the development of a powerful hate, etc. Whether this actually initiates the ulcer or merely activates it, is problematical; more likely, the psychologic insult induces activity. Clinicians have long recognized that a restful holiday can induce a remission even without the conventional dietary regimen. It has been my experience that when a patient is resistant to the Sippy treatment, he is often in a state of mental upheaval; when this is corrected, the symptoms promptly abate.

Indeed, so strong are the interweavings between the psyche and peptic ulcer that a considerable lore has accumulated on the psychogenic origin of peptic ulcer. I have summarized these views (37), but the conclusions are diverse and conflicting. Experimentally, peptic ulcers analogous to those found in the human organism have been produced in animals but only by methods that do not obtain in human beings. Experimentally, the vast majority of observers have succeeded in producing only acute hemorrhagic erosions and because they show no tendency to be limited to the "pathway" and invariably heal promptly, it is unlikely that they represent the forerunners of the true human peptic ulcer. Indeed, the entire issue concerning the pathogenesis of peptic ulcer has been clouded by the uncritical acceptance of the hemorrhagic gastric erosion as the precursor of peptic ulcer. Hemorrhagic erosions are common phenomena at postmortem and are found in association with true peptic ulcer, in sepsis, in peritonitis following abdominal operations (19) in localized sclerosis of a gastric vessel, and following operations upon the brain (13), but proof as yet is not forthcoming that these erosions, any more than the experimental variety, pass into the true Cruveilhier peptic ulcer. As Mann and Bollman (29) state bluntly, "If the mucosal lesion in man which precedes the development of the characteristic peptic ulcer begins as a hemorrhage into the mucosa, it appears that many of the results of our investigations (*v. i.*) would have little if any clinical bearing." Indeed, a considerable part of the experimental research concerning the problem of peptic ulcer has concerned itself with attempts to transform this acute hemorrhagic erosion into the chronic type; the results at best are equivocal. A few have succeeded but by means that are unphysiologic, for instance, by repeated Roentgen ray dosages or by injecting chemical irritants in the neighborhood of the ulcer.

The recent clinical and experimental observations of Bernheim and Penner (44) who showed that hemorrhagic erosions of the gastro-intestinal tract are commonly shock phenomena, have helped I believe to clarify considerably our knowledge of the causes of hemorrhagic erosion both in man and animals.

Their observations certainly make one skeptical of the much quoted neurogenic theory of the origin of peptic ulcer sponsored by Cushing (13), who found that *operations* on the brain were occasionally followed by a gastric erosion. Penner and Bernheim call attention to the frequency of shock after such operations, and in their analysis of postoperative hemorrhagic erosions they also found that shock was a common feature. This probably accounts also for some of the erosions found in association with peptic ulcer with fatal hematemesis (Moschcowitz, Mage and Kugel (38)). The association of true peptic ulcer with erosion does not necessarily justify the conclusion that the erosion was the precursor of the ulcer. In addition to the fact that it may be a shock phenomenon from severe hemorrhage, it may be the result of the associated mucosal inflammatory changes secondary to the peptic ulcer. In brief, no satisfactory evidence has been presented which shows that the hemorrhagic erosion is the earliest phase of peptic ulcer. Hauser (21), who had spent a lifetime studying the genesis and pathology of chronic peptic ulcer, doubts this relationship.

The mechanism whereby the impact of psychologic influences upon a constitutional makeup is transformed into a peptic ulcer has been subject to considerable speculation. Part of the difficulty arises from the fact that, as opposed to hypertension and Graves' disease, we are not in the position to observe transitions, either clinically or in morbid anatomy. Hitherto, the stomach has been clinically an inaccessible organ, the only method of visualization being the Roentgen ray. This method is hardly satisfactory for the purpose of studying natural history because it only demonstrates an ulcer after it has matured. Serial gastroscopy offers a reasonable hope that the earliest lesion of peptic ulcer and its transition may eventually be demonstrated.

The only experimentally produced ulcers that correspond closely to those of the human were produced by Mann and Bollman (29). These ulcers not only occurred exclusively in the "pathway" but grossly and histologically were identical with the true peptic ulcer. They obtained their results in dogs by elimination of the duodenum with the jejunum sewed to the pylorus. If the common bile duct and the pancreatic duct remained implanted into the duodenum, they obtained 20 per cent ulcers; if these ducts were transplanted into the ileum, 50 per cent. If the entire normal mechanism for receiving the gastric contents was eliminated by the functional resection of the duodenum together with the secretion poured into it by the second method, with anastomosis of the proximal end of the jejunum to the terminal ileum, they obtained 95% ulcers. The controlling factor is the acidity. In other words, these methods prevent the neutralization, dilution or buffering of the gastric contents as it passes the stomach. By repeatedly giving hydrochloric acid to normal dogs by continuous drip 8 hours each day, they obtained an ulcer in about 4 weeks. Daily repetition of excess acidity depresses the neutralizing ability. Such ulcers heal in a few days following discontinuance of the acid. In the type of ulcer obtained by elimination of the duodenum and its contents, the ulcer appears rapidly, in hours or less than a day. The morbid anatomy of the primary lesion as given by Mann and Bollman probably represents the prototype of that which, we predict, will

eventually be found in the human stomach. "Macroscopically, they appeared as saucer-like depressions in the mucosa about 2 cm. distal to the pylorus. In their incipience, there is always a ring of mucosa between the ulcer and the pylorus. In the earliest stages, there is a small area covered with a homogeneous gray membrane. When the membrane is sponged off, a slight depression is uncovered where the surface of the mucosa had disappeared and which bled profusely. After the mucosa is eroded the process may proceed quickly until the wall is perforated. Microscopically, the gray membrane is composed of mucosal cell débris. In the earliest stages the injury involves only the tips of the tubules. Hemorrhage then occurs between the tubules underneath the gray covering. As more of the mucosa is injured, leukocytic infiltration occurs, the ulcer penetrates beneath the muscularis mucosa and the ulcer assumes the chronic type (37). Mann and Bollman have apparently solved the problem of chronicity of peptic ulcers, because the agency which prevents their healing persists. These experimental results prove, if nothing more, that the acid factor is vital in the production of ulcer. This has long been surmised clinically by a number of significant observations: 1) Reports of simultaneous association of peptic ulcer and anacidity are so rare that experienced observers like Palmer and Heinz (43) are skeptical that this association exists. 2) Recurrence of either peptic or jejunal ulcers following gastric resection does not result, at least in our experience at The Mt. Sinai Hospital, if complete anacidity is obtained. 3) In the rare cases of ulceration of Meckel's diverticulum, aberrant gastric mucosa is nearly always present and the ulcer is found in the intestinal and not in the gastric portion of the mucosa (3). 4) Peptic ulcer was not found in association with achylia gastrica in over 800 cases of pernicious anemia (26).

In how far do these observations apply to the psychogenic origin of peptic ulcer? In view of the importance of the acid factor, the question arises whether the hyperchlorhydria and hypersecretion so commonly associated with peptic ulcer, especially of the duodenal variety, precede or only follow the initiation of the defect. That emotion may produce temporary hyperchlorhydria is a well-established observation.[4] There are no data available which indubitably establish the presence of hyperchlorhydria in the human previous to the development of an ulcer, but in view of Mann and Bollman's work on the acid factor and the fact that psychic influences cause an increase in acidity and secretion, the probability is strong that continued or reiterated emotional strains do cause a sustained hyperchlorhydria and hypersecretion before the initiation of the ulcer. It seems highly probable therefore that hyperchlorhydria and/or hypersecretion represents one of the intermediary mechanisms between the psyche and the ulcer. In this connection, the experiments of Stahnke (48) and Silverman (47) are convincing. Stahnke showed in dogs that electric stimulation of the vagus nerve, 40 minutes daily for 2 to 3 months, resulted in marked increase in gastric acidity

[4] In a recent publication, Hoelzel (22) who made daily observations upon his gastric acidity over a period of years, found that while he was passing through a period of fear owing to the anticipation of being shot, his acidity rose to appreciable heights. When he moved from his city so that the occasion for fear ceased, his acidity returned to normal.

and peptic activity and, in some instances, a peptic ulcer followed. Silverman found that sham feeding through an esophagostomy opening in the neck caused a powerful stimulation of the peptic glands with large amounts of fluid of a high acid and peptic titre, and eventually the occasional appearance of a peptic ulcer.

Although the discussion in the two following paragraphs is not directly related to the hyperkinetic aspects of peptic ulcer, it is necessary because in many quarters such mechanisms are seriously considered and would tend to negate our thesis.

There is a widely prevalent view that part of the mechanism of the development of peptic ulcer is vascular by way of the vasomotor nerves causing spasms (4, 21, 50), or by narrowing (arteriosclerotic ulcer). Considerable argument and experiment has been expended upon this phase of the problem, but it cannot be said that the results leave a sense of satisfaction. A vascular mechanism for the genesis of peptic ulcer will be difficult to maintain for the following reasons: 1) It is almost impossible to cause an infarct or necrosis in the stomach even by complete closure of a gastric vessel. This is manifest not only experimentally but also in human beings when it becomes necessary in the course of gastric operations to ligate numerous vessels. 2) There is no evidence that the sclerotic vessels so commonly found at the base of a peptic ulcer represent primary changes. They are probably secondary inflammatory lesions. Peptic ulcer is surely not a disease of the decrescent years when vascular occlusions in other parts of the body are common enough. 3) A vascular origin does not explain the remarkable predilection of peptic ulcer for the pathway and the upper duodenum. 4) If we accept the experimental ulcer of Mann and Bollman as the prototype of the human ulcer, there is nothing in their description of the pathogenesis of these ulcers that suggests a primary vascular mechanism. Indeed, as Palmer (42) points out, the fact that the lesion begins in the mucosa and not in the walls, speaks against a vascular mechanism.

Furthermore, the contention of Konjetsny and his school that a chronic gastritis precedes the development of a peptic ulcer must be viewed with much skepticism. Available evidence seems to show that in most instances the gastritis is secondary, the result of chronic infection from the ulcer. When a "gastritis" is present unassociated with ulcer, the histologic criteria, at least as far as I have observed, are remarkably indefinite both in regard to its status as a true inflammation and to its variations from the normal.[5] Other considerations aside, a primary gastritis does not explain the almost human character of peptic ulcer, its limited localization not only to the gastric and upper duodenal mucosa but more particularly, to the "pathway," its great preponderance in males and the rarity of the disease in childhood and in primitive peoples (20). Even assuming that a gastritis may be the background, such an assumption adds nothing to the etiology of peptic ulcer, because the cause of the gastritis

[5] It seems a remarkable fact that the normal histology of the stomach has not been sufficiently studied either in regard to normal deviations, age, the active or resting stage, character of nourishment, race, etc.

is still dark. The same processes of reasoning are applicable in relation to the problem as to whether bacteria, especially streptococci, are responsible for the lesion. In other words, every attempt to explain peptic ulcer as an infection has proven futile.

The relation of psychosomatic factors to the genesis and recurrence of peptic ulcers has significant implications not only on therapy but on prophylaxis. Hurst (23) has pointed out that peptic ulcer has taken the lead as the chief cause of medical disability in British and Canadian soldiers; and Crohn (11) believes, in view of Hurst's report and the rise of peptic ulcer in Finland, that we may expect a rise in the incidence of peptic ulcer in this country in the near future. It is our distinct conviction that there has been an increase in evidence of peptic ulcer in The Mt. Sinai Hospital, especially since the depression of 1929.

As I pointed out some years ago (37) there is a remarkable parallelism between peptic ulcer and Graves' syndrome. In both there is a rather characteristic psychic background, although at times these backgrounds seem to overlap. In Graves' syndrome, the psyche is a highly sensitive and emotional one; in peptic ulcer it is rigid, aggressive and intolerant. In both, a latent malady is brought to light by emotion, either catastrophic or by slow reiterated insults. In both, it is sometimes exceedingly difficult to know when the disease actually begins, but whereas in Graves' syndrome, if one is fortunate, the observer can follow the intensification and increasing tempo of the signs and symptoms from the larval constitutional stage to the formes fruste and finally to the fully blown form, in peptic ulcer, owing to present diagnostic criteria, one can never be sure whether the previously existing chronic indigestion represented an actual ulcer or not. Strictly speaking, therefore, we do not yet know the preceding or intermediate stage of peptic ulcer.[6]

In both, recurrences are common and frequently these recurrences are preceded by emotional upset. In both, excess of normal function dominates the clinical expression of the disease; in both psychic rest is an important adjuvant in therapy, and in both, surgical intervention has parallel indications and results. In Graves' syndrome the operation aims at removing the hyperthyroid element; in peptic ulcer, the elimination of the hyperchlorhydria and the hypersecretion.

4. *Tonus of Cardiac Sphincter.* The increased phase of this tonus is represented in cardiospasm. That there is a normal cardiac sphincter has been demonstrated by Hurst (24), who has coined the term "achalasia" for the persistence of the normal tone of this sphincter which fails to open before the normal peristaltic esophageal wave in the act of swallowing. Cardiospasm may be primary or secondary. Secondary cardiospasm follows various lesions, for instance gastric or esophageal ulcer, gall bladder disease, gastric and esophageal

[6] It should be strongly emphasized that clinical peptic ulcer and peptic ulcer of morbid anatomy are by no means synonymous. It has been shown time and again that peptic ulcer of even considerable dimensions may exist without any clinical evidences whatever. A recurrence of symptoms may not represent the formation of a new ulcer but the activation of a preëxisting one.

neoplasms, etc., but more often cardiospasm is primary. It is needless to enumerate the various causes of primary cardiospasm that have been submitted, because they have not been substantiated by adequate evidence. Most of the hypotheses implicate overstimulation of the vegetative nervous system, either physiologic or as the result of organic changes in the plexus of Auerbach embedded in the walls of the esophagus. The probability is indeed strong that the cardiospasm is mediated through the pathways of the vegetative nervous system, but this is a mechanism and not a cause. Furthermore, it is very probable that the organic degenerative changes witnessed in the Auerbach plexus are not primary but secondary to the ever-present inflammatory changes involving the coats of the esophagus in prolonged cardiospasm. In recent years, evidence has accumulated that primary cardiospasm is psychogenic in origin. The older textbooks all agree that cardiospasm usually occurs in psychoneurotics and that it frequently follows a psychologic trauma. Schindler (46) in his cases unearthed a history of deep anger a day or two before the onset of symptoms. Indeed, in the earliest phases of the cardiospasm he obtained a cure by psychotherapy or hypnosis. Alkan (2) found violent psychic excitement preceding the onset of symptoms. More recently, Winkelstein (54) reported 8 cases in all of which a psychologic trauma initiated the symptoms of cardiospasm.[7] In 2 of his cases, seen in the early phases, psychotherapy resulted in a cure. In the later phases when the cardiospasm is fixed and anatomic changes have occurred, both Winkelstein and Schindler agree that dilatation of the esophagus is essential.

The natural history of cardiospasm is fairly typical. In the early phases, the symptoms come and go with the intervals of well-being becoming progressively shorter. Eventually the difficulty in swallowing becomes constant, the dilatation and tortuosity of the esophagus become progressive and finally pronounced inflammatory and ulcerative lesions ensue with marked hypertrophy of the muscular coat. The intensification of the spasm and the presence of these organic changes account for the failure of psychotherapy in the terminal stages of cardiospasm.

Whether there is a constitutional factor or a characteristic psychologic pattern in patients with cardiospasm requires further observation.

5. *Tonicity, Peristalsis and Secretion of the Colon.* These three normal functions are grouped together because, as a rule, the clinical experiences consequent upon their hyperfunction are associated. The maladies in which these hyperfunctions predominate are mucous "colitis" and non-specific ulcerative colitis.

(*a*) *Mucous "Colitis."* For the following data I am largely indebted to the excellent comprehensive monograph of White, Cobb and Jones (53). The term mucous "colitis" covers not only those conditions in which mucus is constantly passed but a number of conditions in which the passage of mucus is an occasional symptom. These have been described under the appellations of "irritable colon," "spastic constipation," "nervous diarrhea" and "alternating

[7] In the discussion of Winkelstein's paper, Verbrycke referred to a physician who was cured of a cardiospasm by dilatation of the esophagus. He remained well for months but had a prompt recurrence when bandits robbed his bank.

constipation and diarrhea." The malady occurs uncomplicated but is not infrequently associated with other psychosomatic disorders, such as the irritable heart of soldiers (neurocirculatory asthenia), asthma, Graves' syndrome and peptic ulcer. There is no crude correlation with any anthropomorphic type. The sigmoidoscopic picture, while not specific, reveals spasm, dilatation of the superficial venules, the presence of mucus and a somewhat granular appearance of the mucosa. The characteristic radiographic appearance of the colon reveals rapid filling, spasm and irritability, deep haustrations and the string sign. Little is known of its morbid anatomy because patients do not die of this disease. In one case of Mallory's, the goblet cells of the mucosa secreted a large amount of mucus. The patients often reveal vasomotor symptoms mediated through the autonomic nervous system, such as dilation of the pupils, ptyalism or aptyalism, sweating, exaggerated pilomotor responses, sighing respiration and sphincter response. They report that allergy was the cause in only about 4 per cent. In the remainder, emotional tension, acute and chronic, was the cause. Psychologically, White, Cobb and Jones found that asthenia was common. There was high incidence of sexual indifference, two-thirds of the women were frigid and men were satisfied with infrequent intercourse. Minor compulsions existed in a large number—excessive neatness, meticulousness and overconscientiousness. True obsessions were not encountered. These patients ruminated on their problems. Phobias were common, especially of crowds, and they have depressive tendencies. The majority were dependent persons. The emotions most commonly associated were resentment, fear and guilt in that order. They showed difficulty in making decisions. White, Cobb and Jones report experiments in which changes simulating those seen in mucous colitis were produced by drugs which mimicked the action of parasympathetic sacral outflow and the central theme of their exposition is the thesis that "mucous colitis is a physiologic disorder of the colon brought about through the action of the sympathetic nervous system," and that the commonest cause of parasympathetic overstimulation in mucous colitis is emotional tension. This tension was obviously present in 92 per cent of the psychogenic cases in their series. The prognosis for cure is bad because the major emotional problems are usually insoluble. The treatment of such patients consists largely in mental hygiene, including insight, assistance in solving conflicts, social adjustments, disciplinary management, reassurance and transference, suggestion and resolution of the neurosis possibly by a Freudian analysis. In addition, symptomatic therapy may be helpful.

(*b*) *Non-specific Ulcerative Colitis.* Testimony is accumulating that it is a psychosomatic disease. It is tempting to regard non-specific ulcerative colitis as an advanced phase of mucous colitis or spastic colon but thus far the testimony of experienced gastro-enterologists (9, 12, 53) does not permit this conclusion. In my comparatively limited experience, there is no such intermediate clinical phase; the transition from apparent health to the clinical evidence of disease is abrupt. Nevertheless, in a considerable number of patients one can unearth a history that in childhood under the influence of emotional distress, the bowels moved at least 2 or 3 times. Sullivan (49) and Cullinan (12) noted this occur-

rence in a number of their patients with ulcerative colitis and, in others, a history of spastic constipation. Despite the apparent species difference, in non-specific ulcerative colitis as in mucous colitis, all the normal functions of this gut are exaggerated, upon which are superimposed the exudative manifestations of the inflammatory process.

Murray (39) was the first to emphasize the rôle of psychogenic factors in non-specific ulcerative colitis. He reported 12 cases. After commenting that a state of emotion is often accompanied by hypermobility, spasticity, hypersecretion and vasomotor disturbances, he believes that these disturbances can be transmuted into a physical condition, if the emotional conflict is deep seated, or chronic, if there is a specific organism, or if the individual is predisposed by heredity, early training, etc. He found beside fearfulness, emotional immaturity in their mental make-up. Of 7 men, 6 were tied to their mothers and 1 substituted an elder sister for his mother. None were married. Of the 5 women, 3 were married, 1 to a man of her own age. The most frequent conflict arose from the mother attachment and the desire to get married. It is not so much the sudden fright but a new situation which keeps the patient in a state of constant apprehension. Their characters may be described as analerotic with masochism and sadism.

Sullivan (49) reported the psychiatric data on 15 patients. Many of the patients were neat and fussy. Ten patients showed an inability to throw off the effects of an emotional episode. Financial worries occurred in 8 of the 15 and sexual maladjustment was present in all but 2 cases. Five of the males showed abnormal attachments to the mother; in the remaining 5 there was an attachment to some close relative. There is an amazingly close chronologic association between emotional episodes and the onset of the diarrhea. In 11, the bloody diarrhea began within 48 hours of the upset. In the other 4, the emotional state was a prolonged one, but in this group the exacerbation of the diarrhea was as closely dependent on the emotional state as in the first group. Psychotherapy produced striking results when other methods failed.

Wittkower (55) regards ulcerative colitis as a disease of the mentally ill or maladjusted. Almost all of his patients showed character disorders, obvious neurosis or psychosis. He divides his patients into 4 groups: 1) the obsessional—those characterized by overconscientiousness, overscrupulousness, cleanliness and abstinence; 2) the hysterical—those characterized by emotional lability, temper, tantrums, childishness, self-centeredness and suggestibility; 3) a less well-defined group containing some schizothymics and depressives; 4) miscellaneous personality types. In 37 of 40 patients, the colitis or its recurrence was antedated by disturbing events. He also justifies psychotherapy in the treatment of the disease.

Daniels (14) studied 25 cases in the Constitution Clinic at the Presbyterian Hospital. Of 14 cases that were studied intensively comprising 2 men and 12 women, 8 showed a pathologic attachment to a relative; in 6, the death of this relative had been of paramount importance. Indecision concerning marriage was marked in 2 unmarried members of this group and in 2 others engagement

and marriage were the precipitating causes. In 2 cases, the onset of symptoms was associated with childbirth, which also played a prominent rôle in another. Money difficulties were significant in 4 cases. He submits a detailed report of 3 patients. Good results are reported by psychotherapy.

From the psychoanalytic viewpoint, Alexander (1) contrasts the colonic type of patient as dependent, anal receptive and oral aggressive, in contrast to the gastric ulcer type, characterized by "an inner rejection of passive receptive and oral aggression tendencies." Alexander stresses the symbolic use of feces as an expression of hostility, and sometimes as the equivalent of childbirth, an observation noted by Daniels in one of his patients.

In a study of 100 or more cases of non-specific ulcerative colitis in The Mt. Sinai Hospital, I have been strongly impressed by the psychosomatic relationship. As others have noted, there was a close relationship between the onset or exacerbation of symptoms and an emotional upheaval. Indeed, a psychosomatic study is part of the history of every case of ulcerative colitis admitted to The Mt. Sinai Hospital. Often the onset of symptoms was not occasioned by a catastrophic insult but by a prolonged conflict attendant upon a life situation into which the patient found himself propelled. The three dominant life situations that affected these patients were, in the order of frequency, parental fixation, marriage and money, not by any means always sharply demarcated but with interrelationships. Sexual maladjustments were common, as indicated by the frequency in which the onset occurred during and immediately after a honeymoon. There were no apparent anthropologic constitutions, nor was there any particular age incidence, although the majority occurs in the 2d and 3d decades. According to the pediatrists children below the age of 10 are rarely affected.

Psychologically, I have found that they are usually soft and nonaggressive, fussy and overconscientious, sensitive and immature, weak-willed, narrow horizoned and, as White, Cobb and Jones found in mucous colitis, altogether utterly dependent individuals. Like others, I have found that occasionally psychotherapy produces dramatic remissions of the disease, more likely in the early than in the chronic and advanced cases.

The mechanism whereby psychogenic influences produce this serious disease is entirely speculative. It is permissible to state that hyperkinesis is a predominant part of the mechanism and that it is mediated through the pathways of the vegetative nervous system. Experimentally, lesions simulating non-specific ulcerative colitis have not as yet been reproduced. To my view, the most promising lead for the interpretation of the mechanism is that of Lium (27), who made explants of the colon in the abdominal wall. He showed that these explants react to various stimuli by a spastic contraction of the musculature with discharge of mucus and with hemorrhage and ulceration. These stimuli include mechanical stimulation, parasympathomimetic drugs, such as acetylcholine and prostigmine and dysentery toxin. It is conceivable that overstimulation of the vegetative nervous system produced by psychologic influences may produce the same effect as parasympathomimetic drugs. In this connection, it is interesting that White,

Cobb and Jones produced changes in the rectal mucosa stimulating those observed in mucous colitis by the oral administration of acetyl-beta-methylcholine.

Hyperkinesis is well illustrated in the genesis of the psychoses; but these differ from the forementioned hyperkinetic diseases in that, although the sequence from the larval to the labile finally into the fixed stage can be readily traced, morbid anatomic changes, at least thus far, have not been demonstrated.

6. *Manic-depressive Psychosis.* The exaggeration of function that this malady represents may be called the normal rhythm of life, in which the swings between ecstasy and depression are low and to which the average person readily adjusts himself. If one has known a patient intimately before the onset of a manic-depressive psychosis, one can invariably recall that the patient always possessed an abnormal excursion in his emotional range. Indeed, the constitution of the manic-depressive is almost identical with that of Graves' syndrome. The emotions pass from ecstasy to depression in rapid sequence; in fact, the incidence of manic-depressive psychosis in Graves' syndrome is by no means uncommon (5). The patient is high-strung, deeply emotional, narcissistic, violent in his expressions and anxious. He belongs to the type of individual whom I have described as "allergic to life." This type, as I tried to show, is to a large extent the result of environmental influences dating from the earliest years of life, in most instances, maternal overprotection. But there must be a genetic component as well, because all psychiatrists are agreed that manic-depressive psychosis is commonly hereditary (5, 8). As in so many of the hyperkinetic diseases, the pronounced attack of manic-depressive psychosis and its prolonged fixation dates from a sudden emotional strain or prolonged mental conflicts. When the psychosis comes, the individual is not different but an exaggeration and fixation of his former self.

7. *Paranoia.* Paranoia may be regarded as an exaggeration of the normal effective state of the mind. My limited experience with patients whom I have known well and who have developed paranoia has afforded the conviction that I have been observing nothing more than exaggeration and fixation of personality trends. These folk have always been suspicious, eccentric and afflicted with profound obsessions. This impression is confirmed by the observations of experienced psychiatrists. Thus White (52) quotes Mangan as saying, "They show peculiarities during childhood, manifesting themselves in a certain taciturnity, moroseness or disinclination to associate with other children as freely as usual. The child may also have shown a tendency to make friends with an older person, stay at home and read and sew instead of play and may have a tendency to day dreams and the building of air castles." This period may be termed, according to the psychiatrists, the hypochondriacal stage; this is followed by the stage of persecution and finally by the stage of transformation of the personality. Church and Peterson (10) say that paranoia "affects by preference individuals who are even in their childhood, peculiar, morbid, shy, irritable, mistrustful and misanthropic." "Puberty and adolescence tends to intensify the morbid peculiarities already present." Braude (8) comments that from childhood, the makeup of the

paranoic is egocentric, selfish, suspicious, proud and mystic; he is impatient and defiant of conventions. Sadler (45) says that paranoia develops in persons who are suspicious, sensitive, jealous, as well as those who suffer from an inordinate ambition. Paranoid trends are also more likely to develop in shy, dreamy, selfish, prudish and impractical individuals. Sadler and Adolph Meyer (31, 45) even speak of a paranoid constitution. All are agreed that heredity is a strong predisposing factor in paranoia. The mechanism whereby this type personality is transformed into a psychosis is not pertinent to our thesis, nor, indeed, is there any agreement on the part of psychiatrists. But at all events, in this psychosis as in the hyperkinetic diseases that we have discussed the transition can be traced from a basic constitution, conditioned by heredity, to a labile and finally to an intensification and fixation of symptoms.

I am quite sure that I have not exhausted the list of hyperkinetic diseases. For instance, I am confident that the tone of the bronchial musculature plays a rôle in certain forms of asthma of psychogenic origin and that persistent bronchial spasm and compensating phenomena lead to emphysema and eventually to hypertension of the pulmonary circuit and its cardiac sequelæ. Also, I have reason to believe that some forms of schizophrenia subscribe to this pattern. My purpose rather has been to submit a concept. The major problems in the study of the hyperkinetic diseases are: 1) The mechanism whereby the impact of environmental influences upon a constitutional background bring about disease. Inasmuch as the hyperkinetic diseases are essentially human diseases, experimental methods to reproduce them have largely failed because they cannot introduce the human equation. 2) The determination of the reason why one function is predominantly involved. The concept of "organ inferiority" is thus far entirely speculative. The answer probably lies, as Dunbar (18) puts it, "in the various combinations of heredity and constitutional factors, specific conflicts in the course of development, and the total personality organization, plus adventitious factors." White, Cobb and Jones say, "It is not the objective fact of impact which is important but the way in which it is experienced." We may call attention at this point to the fact that there is no specificity between psychosomatic factors and the hyperkinetic function, the proof lying in the not infrequent association in the same patient of two hyperkinetic diseases and indeed of all aspects of psychosomatic medicine. In the solution of these problems the general practitioner possesses a decided advantage over those engaged in exclusive hospital practice because the latter see only a small cross-section, usually the terminal, of the life cycle of the disease. This limitation applies as well to the psychiatrist, although the latter is indispensable in the elucidation and interpretation of the background and the mental workings of the patient. What is needed is a balanced combination of all. It is encouraging that intensive study of the psychosomatic diseases has already been begun in the Psychosomatic Clinic at the Presbyterian Hospital in New York City and the Psychoanalytic Institute in Chicago.

The maladies I have described have common denominators:

*A*. These diseases have as backgrounds a constitution which is usually both

genotypic and phenotypic. The direct stimulus is a maladjustment either sudden or protracted to the trials and tribulations of modern civilized existence. These two factors may be compared as the tinder and the spark, analogous to what occurs in infection.

*B*. There is an exaggeration of function. It is well established that emotion even in the apparently normal being can cause an elevated blood pressure, rise in the basal metabolic rate, an increase in secretion and in the acidity of the stomach, an increase in the tonus of the cardiac sphincter and an increase in the peristalsis and increased secretion of the colon, and it is plausible to assume that if these emotional reactions continue and are profound enough that they may cause a fixation of the hyperkinesis. In all likelihood, this mechanism is mediated through the vegetative nervous system.

Curiously, the only psychosomatic disease I am aware of in which normal functions are depressed is that strange malady known as *anorexia nervosa*. This malady in its severe forms may be regarded as the expression of a wish to die or spiritual suicide. Patients hesitate to take their lives but reduce every item of living to the lowest possible terms. Clinically, though not etiologically and pathologically, it resembles Simmonds' disease and is characterized by profound loss in weight, a subnormal body temperature, a lowered basal metabolic rate, diminished sexual activity, amenorrhea, slow pulse, a lowered blood pressure and hypochlorhydria. Indeed, there are so many features that resemble hibernation, in which the pituitary gland represents part of the mechanism, that one wonders whether the difference between Simmonds' disease and anorexia nervosa consists solely in the fact that in Simmonds' disease the primary change in the pituitary gland is organic and in anorexia functional. The disease appears to be exquisitely psychogenic in origin, most often the result of excessive parental domination. In fact, the disease responds well to psychotherapy. At all events, it is a mystery why in this disease of psychosomatic origin so many of the normal bodily functions should be depressed instead of being elevated.

*C*. These hyperkinetic diseases are essentially human diseases and more particularly of civilization. There is ample testimony that they are rare or uncommon in primitive people and when they do occur in such folk, it is only when they are in competition with the white race. With the exception of peptic ulcer and then only rarely, these diseases have not been observed spontaneously in the lower animals. Nor, indeed, can these methods be satisfactorily reproduced experimentally except by methods that are unphysiologic in the human race.

*D*. These hyperkinetic diseases rarely occur before the age of puberty when the emotive faculties become more subtle and adjustment to life becomes more sensitive and complex.

*E*. These hyperkinetic diseases have an unusual tendency to recur. This is not to be wondered at when one considers that the disease is so closely allied to the ego, and how difficult it is to eliminate completely a normal function of the body. Of all the functions that I have listed the only one that can be eliminated is gastric acidity. If an achlorhydria can be produced by subtotal gastrectomy, one can be assured that the patient will not have a recurrence of his peptic ulcer.

In subtotal thyroidectomy for Graves' syndrome, one removes only part of the total metabolism since the thyroid gland is responsible for only 40 per cent (Means (30)). Recurrence after operation for Graves' disease is always possible, 1) because the personality remains, and 2) because complete adjustment to the old environment has not taken place. Essentially, the treatment of the patient really begins when the operation has been completed.

*F.* Inasmuch as the transition from the normal or static phase to the abnormal is subtle and the line of demarcation is indefinite, there can be no specific diagnostic tests for these diseases, only an arbitrary one. All bodily functions have ranges within the normal, not a precise mathematical quantity. The diagnosis of these diseases therefore depends upon a perspective of the composite picture, in which a study of the personality of the patient and his life history is a vital consideration.

As a rule, the hyperkinetic diseases evolve through 5 discernible stages: 1) the constitutional; 2) the exaggeration of function; 3) the lability of signs and symptoms; 4) the fixation of this exaggerated function; 5) somatic changes. In other words, the time factor is important in the genesis of these diseases. Relativity has its place in medicine as it does in physics.

## SUMMARY

The concept is submitted that certain diseases that may be called "hyperkinetic" represent primary exaggerations of normal bodily functions with morbid anatomic changes as a sequel, instead of the usually accepted reversed order of disease process. Tentatively, the following diseases are submitted: 1) Hypertension of the greater circulation, which represents an exaggeration of the normal intra-arterial pressure and leads to arteriosclerosis and the cardiovascular-renal syndrome. 2) Graves' disease, which represents, in greater part at least, an exaggeration of the normal basal metabolic rate. 3) Peptic ulcer, in which one of the dominant expressions is the exaggerated acidity and secretion of the normal stomach. 4) Cardiospasm, which represents an increase in the normal tone of the cardiac sphincter. 5) "Spastic colon," mucous "colitis" and ulcerative colitis, which represent exaggeration of the normal tonicity, peristalsis and secretion of mucus of the colon. 6) Manic-depressive psychosis, which represents an exaggeration of a normal rhythm. 7) Paranoia, which represents an exaggeration of the affective functions.

The biology of these diseases is discussed and possible mechanisms and new approaches are suggested. These maladies have certain common denominators. They possess a constitution that is usually a combination of phenotypic and genetic characters. The direct stimuli are maladjustments between the psyche and the environment. These diseases are essentially limited to the human species and are mostly products of civilization. Experimentally, they cannot be reproduced in animals except by methods that are unphysiologic for human beings. They rarely occur before the emotive faculties are fully developed. They possess a remarkable tendency to recur. Because the transition from the normal to the abnormal is gradual, no specific diagnostic test is applicable, unless it is an arbi-

trary one. The diagnosis therefore must depend upon a study of the composite picture—the organ—personality. These diseases, as a rule, evolve through 5 stages: 1) constitution; 2) exaggeration of function; 3) a lability of signs and symptoms; 4) fixation of this exaggeration of function; 5) somatic changes.

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